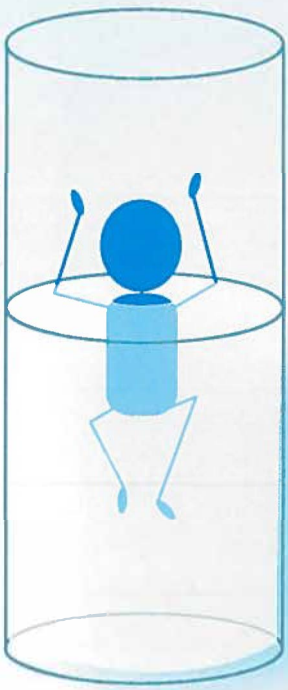
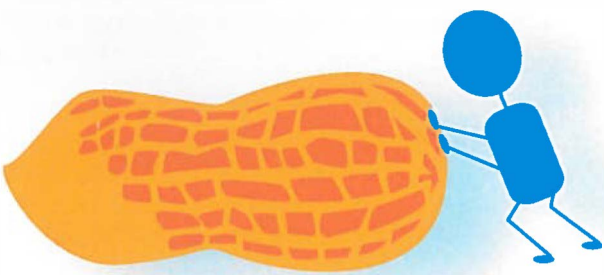
Tina van der Velde

Quality of life of food allergic patients

Kwaliteit van leven van patiënten met voedselallergie





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Stellingen

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Quality of life of food allergic patients

door Tina van der Velde

1. Door voedselallergie neemt de gezondheidsgerelateerde kwaliteit van leven van patiënten met voedselallergie af (dit proefschrift).

2. De voedselallergie en kwaliteit van leven vragenlijsten zijn betrouwbare, valide en responsieve instrumenten om kwaliteit van leven bij patiënten met voedselallergie te meten (dit proefschrift).

3. Ouders van voedselallergische kinderen (8-12 jaar) onderschatten de impact van voedselallergie op de gezondheidsgerelateerde kwaliteit van leven van hun voedselallergische kind (dit proefschrift).

4. De leeftijd van de tiener is een belangrijke voorspeller van verschillen in rapportages tussen voedselallergische tieners en hun ouders wat betreft de impact van voedselallergie op de kwaliteit van leven van de tiener (dit proefschrift).

5. De gezondheidsgerelateerde kwaliteit van leven van de meeste patiënten met voedselallergie verbetert na een dubbelblinde placebogecontroleerde voedselprovocatie en de daarop volgende veranderingen in de behandeling (dit proefschrift).

6. Objectieve maatstaven voor voedselallergie zijn niet zo sterk geassocieerd met gezondheidsgerelateerde kwaliteit van leven als subjectieve maatstaven voor voedselallergie zoals de risico-inschatting en verwachtingen van de patiënt met betrekking tot de uitkomst van een allergische reactie (dit proefschrift).

7. Melk is goed voor elk, behalve voor Jan want die krijgt er netelroos van.

8. Dat is een waarheid als een koe.

9. De huisarts is de spil van de gezondheidszorg.

10. Een mens lijdt het meest door het lijden dat men vreest.

11. Succes is krijgen wat je verlangt. Geluk is houden van wat je hebt.

12. Eten is genieten.

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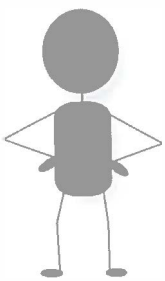
CONTENTS

LIST OF ABBREVIATIONS

CHQ-CF87		Child Health Questionnaire - Child Form
CCC		Concordance Correlation Coefficient
DBPCFC		Double-Blind Placebo-Controlled Food Challenge
EAI		Epinephrine Auto Injector
FAIM	-CF	Food Allergy Independent Measure - Child Form
	-TF	Food Allergy Independent Measure - Teenager Form
	-AF	Food Allergy Independent Measure - Adult Form
	-PF	Food Allergy Independent Measure - Parent Form (parents of children aged 0-12 years)
	-PFT	Food Allergy Independent Measure - Parent Form Teenager version (parents of adolescents aged 13-17 years)
FAQLQ	-CF	Food Allergy Quality of Life Questionnaire - Child Form
	-TF	Food Allergy Quality of Life Questionnaire - Teenager Form
	-AF	Food Allergy Quality of Life Questionnaire - Adult Form
	-PF	Food Allergy Quality of Life Questionnaire - Parent Form (parents of children aged 0-12 years)
	-PFA	Food Allergy Quality of Life Questionnaire - Parent Form Adolescent version (parents of adolescents aged 13-17 years)
FRQL		Food allergy-Related Quality of Life
HRQL		Health-Related Quality of Life
ICC		Intraclass Correlation Coefficient
IPQ		Illness Perception Questionnaire
MID		Minimal Important Difference
NNT		Number Needed to Treat
QoL		Quality of Life
RAND-36		Research and development 36-item Short- Form Health Survey (Dutch translation of the SF-36)
SF-36		The Medical Outcome Study 36-item Short-Form Health Survey
SDC		Smallest Detectable Change
SEM		Standard Error of Measurement
STAI		State and Trait Anxiety Inventory



Chapter 1

General introduction

FOOD ALLERGY

Food allergy is a growing health issue in Western societies and appears to be increasing in prevalence from the late 1990s[1]. About 6 to 8 percent of children suffer from food allergy in the first year of life. The prevalence then falls progressively and remains stable at approximately 3 to 4 percent in adulthood[2]. There are several theories regarding this apparent increase in prevalence. These theories focus on increased hygiene, decreased consumption of omega-3 fatty acids, antioxidants or vitamin D, on dual-allergen exposure and on food processing. However, the exact cause of this apparent increase in prevalence is still unknown[3]. Any food has the potential to cause allergy, although there are certain foods which cause most of them such as milk, egg, peanuts, tree nuts, fish and shellfish. Milk allergy and egg allergy are usually outgrown during childhood, whereas peanut allergy and nut allergy are most likely to persist into adulthood[4].

Food allergy is an abnormal immunologically mediated reaction toward food proteins and may be non IgE-mediated (cellular processes involving T cells and eosinophils) or IgE-mediated (humoral processes involving mast cells and basophils), whereas food intolerances involve all reactions to food that are non-immunologically mediated[5]. Most symptoms of food allergy are caused by mediators released from mast cells and basophils and may involve the skin, oro-pharyngeal tract, gastro-intestinal tract, respiratory tract and cardiovascular system. The variety of symptoms and allergic reactions is great and the disease has an unpredictable nature. People with only mild allergic reactions may have a severe and life-threatening reaction on re-exposure[6]. Food is even the most common trigger of anaphylaxis, which can be fatal[7,8].

At this moment the only proven therapy is to carefully avoid the causal food(s) and to provide medication for emergency treatment. Consequently, an accurate diagnosis is very important in order to identify which foods should be avoided, followed by proper patient education. The most common tools for diagnosing food allergy are physical examination, trial elimination diets, skin-prick tests, allergen-specific IgE testing and oral food challenges[2,9]. A Double-Blind Placebo-Controlled Food Challenge (DBPCFC) is the gold standard for diagnosing food allergy[10]. Currently, there is much research on the development of improved diagnostic tests[11], which are needed to determine the presence and severity of food allergy and to determine whether an allergy is likely to be outgrown or not. Additionally, the development of promising novel treatment strategies, such as immunotherapy[12,13], have caused much excitement. Although immunotherapy has been proven to be successful in venom and respiratory allergies[14], further research is needed before immunotherapy can be used for treating food allergy[15].

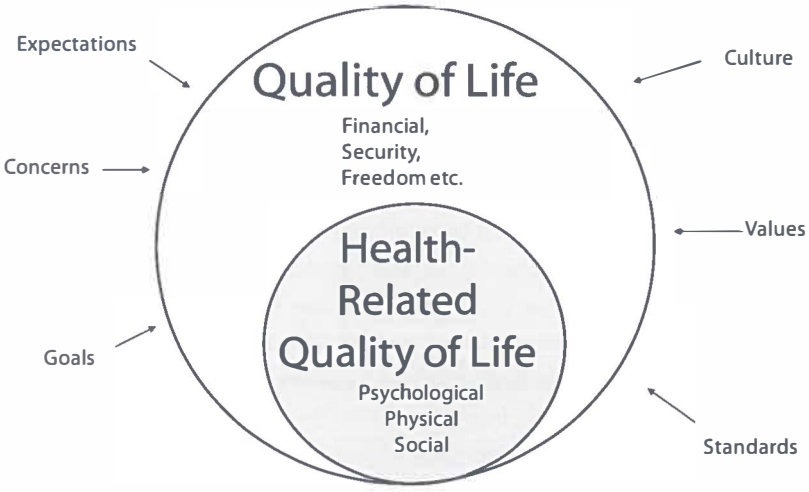
Due to the potentially life-threatening and unpredictable nature of food allergy, accidental exposure may occur and high levels of anxiety of an allergic reaction may exist[6]. Since there is no cure for food allergy, patients are continuously faced with dietary and social restrictions during the day. For example, patients always have to read labels of

food products, which may be time consuming and frustrating, especially when labels are insufficient. Additionally, there is always a chance of accidental exposure, when ingredients of food products are changed or when other people are not aware of the danger of food allergy. Thus, the need for taking precautions to prevent allergen exposure and the fear of an allergic reaction may have a considerable impact on quality of life[16].

HEALTH-RELATED QUALITY OF LIFE (HRQL)

Quality of life is a broad concept and the term is used to evaluate the general well-being of individuals. Quality of life can be described as the subjective value a person places upon satisfaction with his or her own life[17] and includes several different factors such as financial, security, freedom, spiritual contentment, quality of environment, education, health and the way these factors interrelate[18]. As the term quality of life means different things to different people in different cultures, many definitions have been attempted to define this broad and multi-dimensional concept. Quality of life has been defined by the WHO as "the individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns"[19] (figure 1).

Figure 1. The concepts quality of life (QoL) and health-related quality of life (HRQL)



The component of overall quality of life that pertains to an individual's health is called health-related quality of life (HRQL) and includes the psychological, physical and social aspects of one's quality of life that are related to somebody's health. HRQL has been defined by the WHO as a state of complete physical, mental and social well-being and

not merely the absence of disease[19]. Thus, HRQL measures the impact of an illness (and its therapy) on a patient as perceived by the patient and consists of aspects considered important by patients rather than aspects considered important by doctors (figure 1).

NEED FOR MEASURING HRQL IN FOOD ALLERGY

There are several reasons for studying HRQL. Firstly, HRQL measurements give clinicians insight into the impact of a disease on a patient, from a patients perspective and the specific problems a patient has to face. Consequently, clinicians could help food allergic patients managing their specific problems. Additionally, some aspects of food allergy that are considered important by clinicians (for example, objective clinical outcome measures) may not always be the aspects considered important by patients. Moreover, a similar level of objective clinical impairment may have a different impact on HRQL in different patients, because they vary in their illness perceptions[20]. HRQL measurements are the only systematic scientific way to study these differences in HRQL between patients with a similar level of objective clinical impairment and can be used to help each patient coping with their food allergy.

Secondly, HRQL instruments can be used as outcome measure for studying the impact of diagnostic or management interventions from the patient's perspective. Especially in chronic diseases such as food allergy, HRQL may be of special interest, because there is no cure for food allergy and mortality is low. Consequently, such parameters cannot be used as outcome measures. Additionally, no appropriate objective clinical outcome measure is available in food allergy which reflects the ongoing severity of food allergy (such as FEV1 in asthma). One might suggest that the severity of a food allergic reaction can be used as an objective clinical outcome measure for some study purposes. However, a food allergic reaction only occurs intermittently (when a patient is exposed to a culprit food), whereas patients perceive an ongoing burden of food allergy despite the absence of objective symptoms between different food allergic reactions. This ongoing burden can be measured by HRQL instruments. Consequently, HRQL instruments may be an important tool in clinical decision making.

HOW TO MEASURE HRQL

Qualitative and quantitative methods

HRQL can be measured using qualitative methods and quantitative methods. Qualitative research is described as the non-numerical examination and interpretation of observations, usually using a relatively open structure such as narrative description, to discover underlying meanings and patterns and to identify new areas of interest and forming hypotheses. In the context of HRQL, quantitative research may be described as

the numerical representation of observations to describe and explain HRQL. In order to measure HRQL in a quantitative way, validated instruments are needed, because they provide precise outcomes. These instruments may be useful outcome measures in research or clinical practice[21,22].

Quantitative methods: Generic and disease-specific instruments

In order to study HRQL in a quantitative way, a large number of specially designed and tested instruments have been developed for measuring HRQL, which can be divided into two major types of HRQL instruments: generic HRQL instruments and disease-specific HRQL instruments. The type of instrument that is selected for a clinical trial depends on the purpose of the study.

Generic HRQL instruments are intended for general use, irrespective of the disease of the patient. These instruments are useful in evaluating and making comparisons between different diseases. Disadvantages of these instruments are that they are not targeted to issues of particular concern of patients with a specific disease[18,20]. Consequently, they simultaneously measure the impact of co morbid diseases and they are less likely to detect smaller differences in HRQL resulting from a particular disease.

In order to measure HRQL related to a particular disease, disease-specific HRQL instruments are significantly more sensitive than generic ones and are therefore more likely to detect differences in HRQL resulting from a particular disease. These instruments are thus used to investigate and measure disease-specific HRQL problems and are better suited as outcome measure evaluating the impact of interventions for specific diseases[23].

Mostly, only one type of instrument is selected for a clinical trial depending on the purpose of the study. In food allergy, the indications for choosing one instrument over the other, or whether they should be used together, are not known. Therefore, **Chapter 2** discusses the use of generic and disease-specific HRQL in food allergy.

Quantitative methods: Self- and proxy-reported instruments

HRQL can be measured by generic or disease-specific HRQL instruments completed by patients themselves (self-reports) or by instruments completed by external raters such as parents or health-care professionals (proxy-reports). It has been shown that self-reports are often poorly or moderately correlated with proxy-reports and that the patient's view often differs from the view of external raters. In some conditions external raters tend to consistently overestimate HRQL, whereas in other conditions they tend to consistently underestimate HRQL. Additionally, external raters may tend to base their HRQL ratings primarily on physical signs and more obvious symptoms instead of the impact of psychological aspects[18]. Therefore, self-report is the primary method of assessing the subjective aspects of health. Self-reports can be used from the age of 8 years, as these children are able to reliably complete self-reported instruments on the subjective aspects

of health[24,25] and have the necessary language skills and cognitive abilities for accurate self-reporting. Although self-report is the primary method of assessing HRQL, proxy-reports are the only method to measure HRQL in patients who are unable to assess their own HRQL such as very young children, very ill patients or cognitively impaired patients[26].

Additionally, proxy-reports may provide additional information to self-report and may complete the view on a patient's HRQL. On the other hand, it is important to assess the quality of proxy-reporting especially when the parent report is used to provide a substitute for the child's response in children who are unable to self report on their health (too young, too ill or cognitively impaired). It is thus important to study both self- and proxy-reports. Therefore, this is described in **chapter 5 and 6**.

FOOD ALLERGY AND HRQL: WHAT IS KNOWN?

The first well-designed study on the impact of food allergy on HRQL was published in 2000 by Primeau et al.[27]. Since then, HRQL has gradually become an emerging focus of interest in food allergy. The early studies on this topic showed that food allergy has a considerable impact on quality of life of both patients and families in a variety of ways[6,16,27-33]. It was shown that the child's food allergy affected meal preparation, school attendance, familial activities and social activities outside the home (sleepover, birthday parties)[16]. If such activities are restricted, this may interfere with developing social skills and may for some children result in social isolation. It was also shown that general health, parental distress and worry of parents of food allergic children were worse than the general population[29].

Comparing food allergy to other diseases, the early studies showed that parents of peanut allergic children reported significantly more disruption in daily activities, familial problems and social problems than parents of children suffering from rheumatologic disease[27]. Additionally, peanut allergic children reported poorer HRQL and more fear than children with insulin dependent diabetes mellitus[6]. On the other hand, food allergic patients showed less impairment in HRQL than patients suffering from chronic liver disease or irritable bowel syndrome[32]. However, these studies used HRQL scales that were not validated or measured only a single domain of HRQL. A more recent study showed that food allergic patients had poorer generic HRQL than patients with diabetes mellitus, but better generic HRQL than patients with asthma, irritable bowel syndrome and rheumatoid arthritis[34].

A few studies were performed on factors possibly influencing HRQL in food allergic patients. Factors that were associated with poorer HRQL of the child and/or the parent were associated atopic disease[35,36], a higher number of food allergies[16,29,31], female gender[30,37], and having siblings with food allergy[36]. Additionally, younger child age was associated with greater parental anxiety and stress, despite more direct control over the child's diet at younger ages[31]. The presence of parent-reported anaphylaxis was associated with greater

anxiety levels and family impact[31]. However, the opposite has also been shown[16]. The authors suggested that it may be rather the risk of food reactions and measures to avoid them that are associated with lower HRQL rather than the clinical reactivity induced by food intake[36]. However, the exact nature of predictors of HRQL in food allergy still needs further investigation.

Although food allergy is usually over-diagnosed by the public, it may be under-diagnosed by physicians[38]. Nevertheless, it has been shown that food hypersensitivity impairs HRQL regardless of whether the condition had been doctor-diagnosed or not[30]. The authors[30] suggested that this might be explained by the fact that a diagnostic test that verifies allergy says nothing about the individual's experience of the severity of the allergic condition. On the other hand, a diagnostic test ruling out food allergy may prevent unnecessary elimination diets and consequently, may reduce unnecessary deterioration in well-being and deficient nourishment. Therefore, an accurate diagnosis of food allergy is very important and the impact of diagnosis as perceived by the patient needs further investigation **(Chapter 7).**

Although the first studies on food allergy and HRQL revealed some relevant and interesting HRQL issues, these studies also have a couple of limitations. Firstly, most studies focused on parents of food allergic children instead of food allergic children or adolescents themselves[16,27,28,30,35] and data on HRQL of food allergic adults were scarce[27]. Secondly, most studies used non validated disease-specific HRQL instruments for measuring HRQL[6,16,27,30,32] or generic HRQL instruments[30,35], because no appropriate disease-specific HRQL instruments existed for measuring HRQL in food allergic patients as perceived by patient's themselves.

WHICH FOOD ALLERGY SPECIFIC HRQL INSTRUMENTS WERE AVAILABLE?

A few food allergy specific HRQL questionnaires were available before the start of the studies described in this thesis.

Cohen et al. developed the first disease-specific HRQL instrument in 2004, the Food Allergy Quality of Life Parental Burden questionnaire (**FAQL-PB**)[28]. This is an internally valid, reliable and cross-sectionally valid questionnaire for measuring the parental burden of living with a child with food allergy aged 5-18 years. However, this instrument is not longitudinally validated and focuses on the parent's HRQL, not on the patient's HRQL.

Additionally, three other preliminary food allergy specific HRQL instruments were published[6,16,31]. One study assessed the parental adjustment to and coping with children's food allergy using the Food Allergy Parent Questionnaire (**FAPQ**)[31]. This is a brief condition-specific measure that screens for parental anxiety, perceived impact of food allergy, level of family support and coping skills. Another study determined the impact of food allergy

on the daily activities of food allergic children and their families using the Food Allergy Impact Scale (**FAIS**)[16]. This instrument has been developed for children aged 8 months to 17 years and was designed to determine the impact of food allergy on the daily activities of children and their families. Finally, an instrument was developed to compare quality of life of food allergic children with children with diabetes mellitus[6]. However, none of these three instruments has been validated[6,16,31], which is a very important limitation of these studies. Validation is indispensable to determine whether the instrument is really measuring what it is supposed to measure. Moreover, the first two instruments focus[16,31] on the parent's wellbeing rather than the child's wellbeing.

There thus was a need for validated and food allergy specific HRQL instrument's focusing on the patient's HRQL[39].

DEVELOPMENT OF THE FOOD ALLERGY QUALITY OF LIFE QUESTIONNAIRES (FAQLQS)

Recently, a number of food allergy specific health-related quality of life questionnaires (FAQLQs) were developed[40-44] in order to measure HRQL of food allergic patients focusing on the patient's HRQL. These instruments were developed as part of the Europrevall project, a multi-centre research study on food allergy. Different FAQLQs were developed for different age-groups, because it has previously been shown that children, adolescents and adults are developmentally different[45]. Therefore, the experience of food allergy and its subsequent interventions may differ for each age-group as well.

The development of the FAQLQs was performed using established methods involving several phases[46,47]. Firstly, all potential items for the new questionnaires were assembled using patient interviews, literature search and expert opinion (item generation phase). Secondly, the long list with all potentially relevant items was presented to another group of food allergic patients in order to select the items which are considered most important by patients (item reduction phase). These patients were asked to indicate whether an item was applicable to them ("yes" or "no"), and if so, to rate on a five-point scale how troublesome that particular item was. Items identified most frequently and rated the most important were selected for the final FAQLQs. This method is called the clinical impact method[48,49].

In this way three self-administered food allergy specific quality of life questionnaires were developed in the Netherlands for measuring food-allergy related quality of life in children aged 8-12 years (-Child Form, FAQLQ-CF)[40], adolescents aged 13-17 years (-Teenager Form, FAQLQ-TF)[41] and adults aged ≥18 years (-Adult Form, FAQLQ-AF)[42]. Additionally, two parent-administered instruments were developed in Ireland and the UK for measuring the impact of food allergy on the child's HRQL for parents of food allergic children aged 0-12 years (-Parent Form, FAQLQ-PF)[43] and adolescents aged 13-17 years

(-Parent Form, Adolescent version, FAQLQ-PFA)[44] respectively. The latter instruments are thus proxy-reports on the child's HRQL.

Each FAQLQ consists of different items and different domains, because some HRQL items were regarded as important by specific age-groups, but regarded as unimportant and therefore not selected for other age-groups. Some striking similarities and differences were shown for children, adolescents and adults[40-42]. Examples of similar items were: "Able to eat fewer products", "Must always be alert to what you are eating" and "Change of ingredients of a food product". These items were considered important by children, adolescents and adults and therefore included in the FAQLQ-CF, -TF and -AF as well. Examples of age-specific items were: the item "Curious about forbidden products" which was included only for children, the item "Carrying an epinephrine auto-injector" which was only included for adolescents and the item "Incomplete food labels" which was only included for adults.

The FAQLQs are thus disease-specific, age-specific and rater-specific instruments for measuring HRQL in food allergic patients.

RELIABILITY AND VALIDITY OF THE FAQLQS

In developing new instruments it is crucial that these instruments are reliable[50] in order to ensure that the new instruments are dependable and repeatable. Reliability is the degree to which an instrument is free of random error. Classical approaches for examining reliability include internal consistency and reproducibility. Internal consistency refers to what extent all items in the questionnaire measure the same concept. Internal consistency of the FAQLQs was previously measured with Cronbach α[40-42]. Reproducibility measures stability over time when no change in condition has taken place. This is usually assessed using a test-retest study design: Patients, in which no change in condition has taken place, complete the questionnaire twice[51]. Before the start of this thesis, the test-retest reliability of the FAQLQs was unknown. Therefore, the assessment of the reproducibility of the recently developed FAQLQs is described in **chapter 3.**

Additionally, it is important to determine to what degree it is likely that an instrument is measuring what it is intended to measure; i.e. to assess the validity of new instruments[50]. Validation is important because the quality of life items generated in patients and reflecting their areas of concern may not relate to the disease in question. Usually, a new instrument is compared to the true value, a gold-standard, to make it plausible that the new instrument is valid (criterion validity). However, in HRQL research no such a gold standard exists to which a new HRQL questionnaire could be compared, because HRQL instruments measure presumed constructs that are experimental and subjective[18]. Therefore, other methods should be used to establish validity and other instruments should be used to which the new questionnaire can be correlated. For example, convergent and discriminant

validity were established by correlating the FAQLQs with generic HRQL questionnaires[40-42]. Convergent validity refers to what extent the new questionnaire correlates with other measures that are designed to assess similar constructs. Discriminant validity refers to what extent the FAQLQs do not correlate with other measures that are designed to assess dissimilar constructs. However, in order to validate the disease-specificity of an instrument, generic HRQL instruments are inappropriate to correlate the new instrument with.

To assess validity in terms of disease-specificity, an independent measure related to the burden of symptoms characterising the disease is often used, such as the FEV1 in asthma, and this independent measure should correlate with the new instrument. This is called construct validity. As mentioned previously, no independent outcome measure based on symptoms exists reflecting the ongoing severity of food allergy and may even be inappropriate because patients are usually symptom free. As it has previously been shown that the change in the expected outcome of future allergic reactions as perceived by patients, is the source of HRQL changes in anaphylactic disorders[52], we developed an independent measure capable of measuring these "expectations of outcome" and risk perceptions as perceived by the patient. This independent measure is called the Food Allergy Independent Measure (FAIM). The questions of the FAIM capture the perceived expectation of patients of the chance of accidental exposure and the perception of what will happen following accidental exposure. HRQL instruments that were validated using the method of expectation of outcome questions have proved to be useful and consistent in measuring HRQL in anaphylactic disorders[28,46]. The development of the FAIM is described in **chapter 4.**

In order to use the FAQLQs in different cultures, accurate translation and cross cultural validation should take place to check the performance of individual items in that language and culture using established guidelines[53]. A summary of the translation and validation of the FAQLQ-PFs for use in the Netherlands is described in **chapter 5 and 6.**

LONGITUDINAL VALIDITY AND RESPONSIVENESS OF THE FAQLQS

One of the major goals of disease-specific HRQL-instruments is to determine the impact of interventions on HRQL from a patient's perspective. Therefore, HRQL instruments that will be used as outcome measures must correlate over time with other relevant measures (longitudinal validity) and must be able to measure small but relevant HRQL changes over time (responsiveness)[54,55]. The longitudinal validity and responsiveness of the FAQLQs were not yet established at the start of this study. Assessing longitudinal validity and responsiveness can be performed in patients in whom HRQL is expected to change because of diagnostic or therapeutic interventions. For example, improved diagnosis, counseling and expert dietary guidance are interventions that are expected to change HRQL of food allergic patients. **Chapter 7** describes the longitudinal validation and

responsiveness of the FAQLQ-CF, -TF and -AF using a Double-Blind Placebo-Controlled Food Challenge (DBPCFC) and its subsequent changes in management as an intervention.

IMPACT OF DOUBLE-BLIND PLACEBO-CONTROLLED FOOD CHALLENGES (DBPCFC)

Since the only available treatment for food allergy is strict avoidance of the culprit foods, an accurate diagnosis is very important to identify which foods should be avoided. Additionally, an accurate diagnosis ruling out food allergy may prevent unnecessary elimination diets and consequently, may reduce unwanted and unnecessary deterioration in HRQL, anxiety and deficient nourishment. A Double-Blind Placebo-Controlled Food Challenge (DBPCFC) is thus an important tool in the management of food allergy. A DBPCFC is considered to be a time-consuming process and suspected to be potentially burdensome and stressful to patients, because potential severe reactions may occur during food challenge. Although some studies have recently been published describing the impact of a DBPCFC on the child from the parent's perspective[55-60], the impact of undergoing a DBPCFC from the patients' perspective remains unclear. It is thus important to study the impact of a DBPCFC on HRQL from the patient's perspective.

The recently published studies[55-60] on the parent's perspective of the impact of their child's food challenge, showed that the child's HRQL improved significantly[43], that parental concerns[56,57] and anxiety[60] were reduced and that most of the parents were satisfied[57] following a food challenge irrespective of the outcome. The authors suggested that these improvements in HRQL/wellbeing were caused by the fact that a definitive diagnosis provides a sense of certainty[55,56], because uncertainty and lack of information were considered to be more worrisome than fear of the challenge procedure. However, the impact of a DBPCFC on HRQL from the patient's perspective still remains unclear. Therefore, this is described in **chapter 7.**

AIMS OF THIS THESIS

This thesis continues the studies on the development and cross-sectional validation of the FAQLQ-CF, -TF and -AF published by Flokstra-de Blok et al.[40-42], the FAQLQ-PF published by Dunn Galvin et al[43] and the FAQLQ-PFA[44]. The aim of this thesis was to assess some important psychometric properties (reliability, longitudinal validity and responsiveness) of the FAQLQs for children, adolescents and adults and to translate and validate the FAQLQ-PF and FAQLQ-PFA for use in the Netherlands. Additionally, the instruments were used to get insight into different aspects of the HRQL of food allergic patients such as differing views between parents and their children on the child's HRQL and to evaluate the impact of a DBPCFC from the patient's perspective.

OUTLINE OF THIS THESIS

In **Chapter 2** the terms generic and disease-specific HRQL are introduced in the context of food allergy. A comparison is made between generic and disease-specific HRQL of food allergic children, adolescents and adults using generic and disease-specific HRQL instruments. Additionally, suggestions are given for choosing one instrument over the other.

Chapter 3 is the first article of this thesis concerning the psychometric properties of the FAQLQs. This chapter describes the reliability of the FAQLQ-CF, -TF and -AF using a test-retest reliability study design.

Chapter 4 is related to the validation of the FAQLQs and describes the development of the instrument we used for validation of the FAQLQs. This instrument is called the Food Allergy Independent Measure (FAIM), which is based on the perceived risks and expectations of patients concerning the outcome of an allergic reaction. Such risk perceptions and expectations are known to be important predictors of HRQL and should therefore correlate with HRQL. Such a correlation makes the validity of the FAQLQs, which is an ongoing process, more likely.

Chapter 5 gives insight into differing views between parents and their food allergic children on the child's HRQL. Additionally, a summary of the translation and validation process of the FAQLQ-PF for use in the Netherlands is described.

In line with the previous chapter, **chapter 6** describes disagreement in views between parents and adolescents regarding the adolescent's HRQL. Food allergic adolescents require special attention and need to be analyzed separately, because adolescents are developmentally different, behave differently, use different coping strategies and are of greatest risk for anaphylaxis. Do differences in views between parents and adolescents on the adolescent's HRQL give additional insight into the problems adolescents have to cope with?

In **chapter 7** the longitudinal validity and the responsiveness of the FAQLQs are demonstrated. Additionally, the impact of a DBPCFC on HRQL as perceived by the patient is described.

Finally, in **chapter 8** the results of the previous chapters are discussed resulting in an overview of this thesis. Additionally, implications for future research will be given.

REFERENCE LIST

1. Sicherer SH, Munoz-Furlong A, Godbold JH, Sampson HA. US prevalence of self-reported peanut, tree nut, and sesame allergy: 11-year follow-up. J Allergy Clin Immunol 2010; 125:1322-6.
2. Sicherer SH, Sampson HA. Food allergy. J Allergy Clin Immunol 2010; 125(2 Suppl 2):S116-25.
3. Lack G. Update on risk factors for food allergy. J Allergy Clin Immunol 2012; 129:1187-97.
4. Dannaeus A, Inganas M. A follow-up study of children with food allergy. clinical course in relation to serum IgE- and IgG-antibody levels to milk, egg and fish. Clin Exp Allergy 1981; 11:533-9.
5. Johansson SG, Bieber T, Dahl R, et al. Revised nomenclature for allergy for global use: Report of the nomenclature review committee of the world allergy organization, october 2003. J Allergy Clin Immunol 2004; 113:832-6.
6. Avery NJ, King RM, Knight S, Hourihane JO. Assessment of quality of life in children with peanut allergy. Pediatr Allergy Immunol 2003; 14:378-82.
7. Sampson HA. Food-induced anaphylaxis. Novartis Found Symp 2004; 257:161-71; discussion 171-6, 207-10, 276-85.
8. Boden SR, Wesley Burks A. Anaphylaxis: A history with emphasis on food allergy. Immunol Rev 2011; 242:247-57.
9. Lock RJ, Unsworth DJ. Food allergy: Which tests are worth doing and which are not? Ann Clin Biochem 2011; 48:300-9.
10. Bock SA, Sampson HA, Atkins FM, et al. Double-blind, placebo-controlled food challenge (DBPCFC) as an office procedure: A manual. J Allergy Clin Immunol 1988; 82:986-97.
11. Beyer K, Ellman-Grunther L, Jarvinen KM, Wood RA, Hourihane J, Sampson HA. Measurement of peptide-specific IgE as an additional tool in identifying patients with clinical reactivity to peanuts. J Allergy Clin Immunol 2003; 112:202-7.
12. Mousallem T, Burks AW. Immunology in the clinic review series; focus on allergies: Immunotherapy for food allergy. Clin Exp Immunol 2012; 167:26-31.
13. Kulis M, Vickery BP, Burks AW. Pioneering immunotherapy for food allergy: Clinical outcomes and modulation of the immune response. Immunol Res 2011; 49:216-26.
14. Finegold I, Dockhorn RJ, Ein D, Dolen WK, Oppenheimer J, Potter LH. Immunotherapy throughout the decades: From noon to now. Ann Allergy Asthma Immunol 2010; 105:328-36; quiz 337, 358.
15. Beyer K. A european perspective on immunotherapy for food allergies. J Allergy Clin Immunol 2012; 129:1179-84.
16. Bollinger ME, Dahlquist LM, Mudd K, Sonntag C, Dillinger L, McKenna K. The impact of food allergy on the daily activities of children and their families. Ann Allergy Asthma Immunol 2006; 96:415-21.
17. Thompson AK, Juniper E, Meltzer EO. Quality of life in patients with allergic rhinitis. Ann Allergy Asthma Immunol 2000; 85:338,47; quiz 347-8.
18. Fayers PM, Machin D. Quality of life : The assessment, analysis and interpretation of patient-reported outcomes. 2nd ed. Chichester etc.: Wiley; 2007.
19. World Health Organisation. Constitution of the World Health Organisation. Handbook of basic documents. In: Geneva: ; 1948. p. 3-20.
20. Guyatt GH, Feeny DH, Patrick DL. Measuring health-related quality of life. Ann Intern Med 1993; 118:622-9.
21. Flokstra-de Blok BM, Dubois AE. Quality of life measures for food allergy. Clin Exp Allergy 2012; 42:1014-20.
22. Casebeer AL, Verhoef MJ. Combining qualitative and quantitative research methods: Considering the possibilities for enhancing the study of chronic diseases. Chronic Dis Can 1997; 18:130-5.
23. Jenney ME, Campbell S. Measuring quality of life. Arch Dis Child 1997; 77:347-50.
24. Riley AW. Evidence that school-age children can self-report on their health. Ambul Pediatr 2004; 4:371-6.
25. Cremeens J, Eiser C, Blades M. Characteristics of health-related self-report measures for children aged three to eight years: A review of the literature. Qual Life Res 2006; 15:739-54.
26. Connolly MA, Johnson JA. Measuring quality of life in paediatric patients. Pharmacoeconomics 1999; 16:605-25.
27. Primeau MN, Kagan R, Joseph L, et al. The psychological burden of peanut allergy as perceived by adults with peanut allergy and the parents of peanut-allergic children. Clin Exp Allergy 2000; 30:1135-43.

28. Cohen BL, Noone S, Munoz-Furlong A, Sicherer SH. Development of a questionnaire to measure quality of life in families with a child with food allergy. J Allergy Clin Immunol 2004; 114:1159-63.
29. Sicherer SH, Noone SA, Munoz-Furlong A. The impact of childhood food allergy on quality of life. Ann Allergy Asthma Immunol 2001; 87:461-4.
30. Marklund B, Ahlstedt S, Nordstrom G. Health-related quality of life among adolescents with allergy-like conditions - with emphasis on food hypersensitivity. Health Qual Life Outcomes 2004; 2:65.
31. Lebovidge JS, Stone KD, Twarog FJ, et al. Development of a preliminary questionnaire to assess parental response to children's food allergies. Ann Allergy Asthma Immunol 2006; 96:472-7.
32. Calsbeek H, Rijken M, Bekkers MJ, Kerssens JJ, Dekker J, van Berge Henegouwen GP. Social position of adolescents with chronic digestive disorders. Eur J Gastroenterol Hepatol 2002; 14:543-9.
33. Teufel M, Biedermann T, Rapps N, et al. Psychological burden of food allergy. World J Gastroenterol 2007; 13:3456-65.
34. Flokstra-de Blok BM, van der Velde JL, Vlieg-Boerstra BJ, et al. Health-related quality of life of food allergic patients measured with generic and disease-specific questionnaires. Allergy 2010; 65:1031-8.
35. Sicherer SH. Diagnosis and management of childhood food allergy. Curr Probl Pediatr 2001; 31:35-57.
36. Marklund B, Ahlstedt S, Nordstrom G. Health-related quality of life in food hypersensitive schoolchildren and their families: Parents' perceptions. Health Qual Life Outcomes 2006; 4:48.
37. DunnGalvin A, Hourihane JO, Frewer L, Knibb RC, Oude Elberink JN, Klinge I. Incorporating a gender dimension in food allergy research: A review. Allergy 2006; 61:1336-43.
38. Marklund B, Ahlstedt S, Nordstrom G. Food hypersensitivity and quality of life. Curr Opin Allergy Clin Immunol 2007; 7:279-87.
39. de Blok BM, Vlieg-Boerstra BJ, Oude Elberink JN, et al. A framework for measuring the social impact of food allergy across europe: A EuroPrevall state of the art paper. Allergy 2007; 62:733-7.
40. Flokstra-de Blok BM, DunnGalvin A, Vlieg-Boerstra BJ, , et al. Development and validation of a self-administered food allergy quality of life questionnaire for children. Clin Exp Allergy 2009; 39:127-37.
41. Flokstra-de Blok BM, DunnGalvin A, Vlieg-Boerstra BJ, et al. Development and validation of the self-administered food allergy quality of life questionnaire for adolescents. J Allergy Clin Immunol 2008; 122:139-44, 144.e1-2.
42. Flokstra-de Blok BM, van der Meulen GN, DunnGalvin A, et al. Development and validation of the food allergy quality of life questionnaire - adult form. Allergy 2009; 64:1209-17.
43. DunnGalvin A, de BlokFlokstra BM, Burks AW, Dubois AE, Hourihane JO. Food allergy QoL questionnaire for children aged 0-12 years: Content, construct, and cross-cultural validity. Clin Exp Allergy 2008; 38:977-86.
44. Hamp N, Hourihane J, Knibb RC, Dubois AEJ, Flokstra-de Blok BMJ, DunnGalvin A. Developmental specificity and sensitivity between two age appropriate health-related quality of life measures in food allergic children and teenagers. J Allergy Clin Immunol 2008; 121:S107.
45. DunnGalvin A, Hourihane JB. Developmental trajectories in food allergy: A review. Adv Food Nutr Res 2009; 56:65-100.
46. Oude Elberink JN, de Monchy JG, Golden DB, Brouwer JL, Guyatt GH, Dubois AE. Development and validation of a health-related quality-of-life questionnaire in patients with yellow jacket allergy. J Allergy Clin Immunol 2002; 109:162-70.
47. Juniper EF, Guyatt GH, Jaeschke R. How to develop and validate a new health-related quality of life instrument. In: Spilker B, ed. Quality of life and pharmacoeconimcs in clinical trials. Philadelphia: Lippincott-Raven Publishers; 1996. p. 49-56.
48. Juniper EF, Guyatt GH, Dolovich J. Assessment of quality of life in adolescents with allergic rhinoconjunctivitis: Development and testing of a questionnaire for clinical trials. J Allergy Clin Immunol 1994; 93:413-23.
49. Juniper EF, Guyatt GH, Epstein RS, Ferrie PJ, Jaeschke R, Hiller TK. Evaluation of impairment of health related quality of life in asthma: Development of a questionnaire for use in clinical trials. Thorax 1992; 47:76-83.
50. Testa MA, Simonson DC. Assesment of quality-of-life outcomes. N Engl J Med 1996; 334:835-40.
51. Schuck P. Assessing reproducibility for interval data in health-related quality of life questionnaires: Which coefficient should be used? Qual Life Res 2004; 13:571-86.
52. Oude Elberink JN. Significance and rationale of studies of health-related quality of life in anaphylactic disorders. Curr Opin Allergy Clin Immunol 2006; 6:298-302.
53. Process of translation and adaptation of instruments. http://www.who.int/substance_abuse/research_tools/translation/en/ [homepage on the Internet]. 2008.

54. Oude Elberink JN, De Monchy JG, Van Der Heide S, Guyatt GH, Dubois AE. Venom immunotherapy improves health-related quality of life in patients allergic to yellow jacket venom. J Allergy Clin Immunol 2002; 110:174-82.

55. DunnGalvin A, Cullinane C, Daly DA, Flokstra-de Blok BM, Dubois AE, Hourihane JO. Longitudinal validity and responsiveness of the food allergy quality of life questionnaire - parent form in children 0-12 years following positive and negative food challenges. Clin Exp Allergy 2010; 40:476-85.

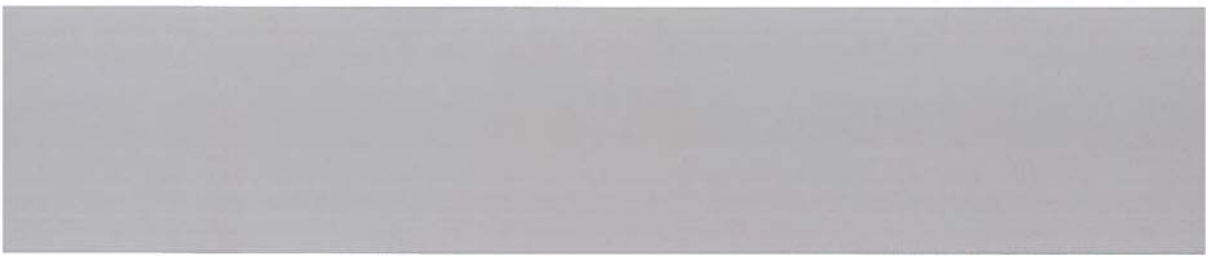
56. Kemp AS, Allen CW, Campbell DE. Parental perceptions in egg allergy: Does egg challenge make a difference? Pediatr Allergy Immunol 2009; 20:648-53.

57. Nguyen M, Wainstein BK, Hu W, Ziegler JB. Parental satisfaction with oral peanut food challenges; perception of outcomes and impact on management of peanut allergy. Pediatr Allergy Immunol 2010; 21:1119-26.

58. Strinnholm A, Brulin C, Lindh V. Experiences of double-blind, placebo-controlled food challenges (DBPCFC): A qualitative analysis of mothers' experiences. J Child Health Care 2010; 14:179-88.

59. Knibb RC, Ibrahim NF, Stiefel G, et al. The psychological impact of diagnostic food challenges to confirm the resolution of peanut or tree nut allergy. Clin Exp Allergy 2012; 42:451-9.

60. Zijlstra WT, Flinterman AE, Soeters L, et al. Parental anxiety before and after food challenges in children with suspected peanut and hazelnut allergy. Pediatr Allergy Immunol. 2010; 21(2 Pt 2):e439-45.



Chapter 2

Health-related quality of life of food allergic patients measured with generic and disease-specific questionnaires

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ABSTRACT

Objective: Health-Related Quality of Life (HRQL) has never been measured with both generic and disease-specific questionnaires in the same group of food allergic patients. The aim of this study was to compare HRQL of food allergic patients as measured with generic and disease-specific questionnaires.

Methods: Generic questionnaires (CHQ-CF87 and RAND-36) and disease-specific HRQL questionnaires (FAQLQ-CF, -TF and -AF) were completed by 79 children, 74 adolescents and 72 adults with food allergy. Floor and ceiling effects, percentage of agreement and multivariate stepwise regression analysis were used to compare the generic and disease-specific measurements.

Results: The FAQLQs showed minimal floor or ceiling effects. The CHQ-CF87 and RAND-36 showed minimal floor effects, but remarkable ceiling effects (>73%) were found for the scales role functioning-emotional (RE), role functioning-behaviour (RB), role functioning-physical (RP) in children and adolescents and the scale RE (>79%) in adults. Additionally, we found low percentages of agreement between the generic and disease-specific questionnaires to identify the same food allergic patients with the best or worst HRQL. Only patients with the best disease-specific HRQL also tended to have the best generic HRQL. Finally, the explained variance in HRQL by patient characteristics was higher in the disease-specific questionnaires (30.7% to 62.8%) than in the generic scales (6.7% to 31.7%).

Conclusions: Disease-specific HRQL questionnaires may be more suitable to measure clinically important impairments in HRQL or HRQL differences over time in food allergic patients. However, generic HRQL questionnaire are indispensable for the comparison between different diseases and are thus complementary.

INTRODUCTION

Although food allergic patients may experience symptoms only intermittently, they must maintain a high degree of vigilance in order to prevent exposure to foods to which they are allergic. This may be a great burden to themselves and their families[1,2]. Despite taking precautions, there is always a chance of accidental exposure and for some patients such exposure may be fatal[3]. Consequently, food allergy has a significant impact on health-related quality of life (HRQL)[4].

HRQL can be measured with two types of questionnaires: generic and disease-specific questionnaires. Generic questionnaires can be used to evaluate and compare different diseases. The disadvantages of generic questionnaires are that they may not focus adequately on problems specific to a particular disease and that they simultaneously measure the impact of comorbid diseases. Disease-specific instruments, as their name implies, are targeted to a specific disease. These disease-specific questionnaires are more likely to detect clinically important impairments specific for a particular disease or HRQL differences over time. However, disease-specific questionnaires do not allow direct comparison between different diseases[5]. In food allergy, HRQL is the only available measure that reflects the ongoing perceived severity of this disorder, since no objective disease parameters are available that reflect the ongoing severity[6].

In food allergy research, a number of studies have investigated the impact of food allergy on HRQL[7-15]. Only one of these studies used both generic and disease-specific questionnaires in food allergic children[13]. However, the disease-specific questionnaire used in that study was not assessed for validity and reliability. Since valid and reliable self-administered disease-specific HRQL questionnaires for food allergic patients have become available only recently[16-19], the administration of both generic and disease-specific instruments to the same population of food allergic patients is now possible.

Therefore, the aim of this study was to investigate the impact of food allergy on HRQL as measured with generic and disease-specific questionnaires in children (8 to 12 years), adolescents (13 to 17 years) and adults (≥18 years).

METHODS

Participants

The children (8-12 years), adolescents (13-17 years) and adults (≥18 years) that participated in the present study were part of the studies on the cross-sectional validation of the Food Allergy Quality of Life Questionnaire-Child Form, -Teenager Form and -Adult Form (FAQLQ-CF, -TF and -AF)[17-19]. These participants had a physician-diagnosed food allergy for at least one food, and were recruited from our outpatient (paediatric) allergy clinic or were recruited through food allergy support organisations (the Dutch Foundation for Food

Allergy and the Dutch Anaphylaxis Network) and by advertisement in local newspapers. Forty-seven children (59%), 43 adolescents (58%) and 42 adults (58%) were recruited from our allergy outpatient clinic. The food allergy was confirmed by a double-blind placebo-controlled food challenge (DBPCFC) in 25 children (31%), 19 adolescents (26%) and 14 adults (19%). The other patients had a physician-diagnosed food allergy based on history and skin prick and/or blood test. The majority of them were awaiting a DBPCFC. All patients recruited by advertisement (32 children [41%], 31 adolescents [42%] and 30 adults [42%]) reported physician-diagnosed food allergies. The most common types of food allergies and different types and severities of symptoms were represented in the study sample. The study was reviewed by the local medical ethical committee (METc 2005/051) who deemed that approval was not needed.

Procedure

The HRQL questionnaires (the age appropriate generic and disease-specific questionnaire), the Food Allergy Independent Measure (FAIM)[20] and descriptive questions on age, sex, type and number of food allergies, type of symptoms and diagnosis were sent by mail to be completed at home. Participants were not paid for their participation. The children (8 to 12 years) and their parents were instructed that the children should fill out the questionnaires by themselves. Parents were allowed to explain a question when needed, but they were not allowed to tell the child which answer to give. For completing the descriptive questions parents were allowed to help their child when needed. The FAIM measures the patients' perceived expectation of outcome. It was used as a validation measure in the studies on the development and validation of the FAQLQs[17-19].

Questionnaires

Generic HRQL questionnaires

In children and adolescents, the Child Health Questionnaire-Child Form (CHQ-CF87) was administered[21,22]. This questionnaire is self-administered by the child and contains 87 items divided into twelve scales (Table 1). After recoding the raw scores, scale scores are computed and transformed into a 100-point scale. Higher scores indicate better HRQL.

In adults we administered the RAND-36, which is the Dutch translation of the MOS 36-item Short-Form Health Survey[23,24]. The RAND-36 consists of 36 items divided into nine scales (Table 1). After recoding the raw scores, scale scores are computed and transformed into a 100-point scale. Higher scores indicate better HRQL.

Table 1. Scales of the generic and disease-specific HRQL questionnaires, number of items and the mean (SD) score in food allergic patients

HRQL questionnaires	Abbreviation Domain	No. of items	Mean (SD)	
CHQ-CF87[1] (Children and adolescents)			**Children**	**Adolescents**
Physical functioning	PF	9	96.0 (8.2)	94.4 (10.5)
Role functioning-emotional	RE	3	94.9 (14.3)	91.4 (18.4)
Role functioning-behaviour	RB	3	95.1 (12.7)	94.3 (15.4)
Role functioning-physical	RP	3	94.9 (14.2)	92.9 (20.9)
Bodily pain	BP	2	76.8 (24.7)	70.0 (23.3)
General behaviour	BE	17	84.0 (12.5)	80.6 (10.4)
Mental health	MH	16	78.5 (13.1)	74.6 (13.7)
Self-esteem	SE	14	79.4 (13.8)	70.8 (14.4)
General health	GH	12	72.0 (19.2)	64.4 (18.8)
Family activities	FA	6	86.9 (14.7)	84.8 (16.1)
Family cohesion	FC	1	80.9 (18.6)	73.4 (21.3)
Change in health[2]	CH	1		
RAND-36 (SF-36)[1] (Adults)			**Adults**	
Physical functioning	PF	10	86.1 (18.9)	
Social functioning	SF	2	75.5 (23.8)	
Role functioning-physical	RP	4	70.8 (40.2)	
Role functioning-emotional	RE	3	83.8 (34.0)	
Mental health	MH	5	75.2 (16.1)	
Vitality	VT	4	60.1 (19.0)	
Bodily pain	BP	2	79.4 (22.4)	
General health	GH	5	56.8 (23.1)	
Change in health[2]	CH	1		
FAQLQ-CF[3] (Children)		24	3.96 (1.41)	
Allergen avoidance	AA	7	3.62 (1.56)	
Risk of accidental exposure	RAE	5	4.18 (1.73)	
Emotional impact	EI	6	4.00 (1.70)	
Dietary restrictions	DR	6	4.21 (1.56)	
FAQLQ-TF[3] (Adolescents)		23	4.15 (1.18)	
Allergen avoidance and dietary restrictions	AADR	10	3.96 (1.38)	
Risk of accidental exposure	RAE	6	4.19 (1.30)	
Emotional impact	EI	7	4.40 (1.47)	
FAQLQ-AF[3] (Adults)		29	4.48 (1.31)	
Allergen avoidance and dietary restrictions	AADR	11	4.90 (1.37)	
Risk of accidental exposure	RAE	8	4.34 (1.44)	
Emotional impact	EI	7	4.47 (1.61)	
Food allergy related health	FAH	3	3.78 (1.73)	

[1] The CHQ-CF87 and RAND-36 (SF-36) scores are based on a 100-point scale, where 100 is the best possible score (best HRQL).
[2] Not used in this study.
[3] The FAQLQ-CF, -TF and -AF scores are based on a 7-point scale, where 1 is the best possible score (best HRQL).

Disease-specific HRQL questionnaires

The disease-specific HRQL questionnaires used in this study were the FAQLQ-CF for children aged 8-12 years, the FAQLQ-TF for adolescents aged 13-17 years and the FAQLQ-AF for adults aged 18 years and older[17-19]. All three questionnaires were validated in the Netherlands and showed excellent reliability[25]. These questionnaires consist of 24, 23 and 29 items, respectively, divided into 4, 3 and 4 domains (Table 1). The raw FAQLQ scores 0 to 6 were recoded as 1 to 7. The total score is the mean of all items of each questionnaire and ranges from 1 (minimal impairment of HRQL) to 7 (maximal impairment of HRQL). Thus higher scores indicate poorer HRQL.

Statistical analysis

Statistical analyses were performed with SPSS for Windows 14.0 (SPSS Inc., Chicago, IL, USA). Domain scores for the CHQ-CF87[21] and RAND-36[23] were calculated and total scores and domain scores were calculated for the FAQLQs[17-19]. Additionally, floor and ceiling effects (percentage of patients with the minimal or maximal score, respectively) of the generic and disease-specific questionnaires were investigated. The floor and ceiling of the generic CHQ-CF87 and RAND-36 were a score of 0 and 100, while these were a score of 1 and 7 for the disease-specific FAQLQs. To investigate whether generic and disease-specific HRQL questionnaires identify the same patients, we identified the 10% of patients with the best HRQL and the 10% of patients with the worst HRQL as measured with the generic and disease-specific questionnaires and compared these. Finally, to investigate the extent to which patient characteristics explain generic and disease-specific HRQL, we performed multivariate stepwise regression analysis. The disease-specific FAQLQs and two scales of the generic CHQ-CF87 and RAND-36 were used as dependent variables. The patient characteristics were used as independent variables. Adjusted R^2 was used to describe the degree of variance in HRQL explained by the model in percentage. We choose the two generic scales with the highest and the lowest correlation with the disease-specific FAQLQs[17-19], because these scales indicate the generic scales with the most and least agreement with the disease-specific FAQLQs, respectively.

RESULTS

Participants

The questionnaire packages including the FAQLQs and the age appropriate generic HRQL questionnaires were sent to 312 participants divided over the three age groups. Response rates were high: children 84/114 (73%), adolescents 75/98 (77%) and adults 80/100 (80%). A few returned questionnaires were excluded from the analysis because a) no current food allergies were reported (three children and one adult) or b) no physician-diagnosed food allergy was reported (seven adults) or c) the descriptive characteristics were missing (one

child and one adolescent) or d) the generic questionnaire was not completed (one child). Therefore, 225 participants were included in the final analysis. The mean (SD) scores of the CHQ-CF87, RAND-36 and FAQLQs are shown in Table 1. Table 2 shows the descriptive characteristics of the participants.

Table 2. Descriptive characteristics of the food allergic participants.

	Children	Adolescents	Adults
Patients, n	79	74	72
Sex, m/f	45/34	34/40	18/54
Age, mean (SD), years	10.2 (1.3)	14.7 (1.3)	37.2 (14.3)
Age range (years)	8-12	13-17	18-72
Type of food allergies, n (%)			
Peanut	59 (74)	57 (77)	42 (58)
Tree nut	57 (72)	56 (76)	42 (58)
Egg	29 (37)	26 (35)	16 (22)
Milk	22 (28)	29 (39)	19 (26)
Fish	2 (3)	13 (18)	11 (15)
Shell fish	7 (9)	12 (16)	12 (17)
Wheat	10 (13)	5 (7)	12 (17)
Sesame	14 (18)	8 (11)	13 (18)
Soy	12 (15)	17 (23)	13 (18)
Celery	1 (1)	3 (4)	11 (15)
Fruits	29 (37)	38 (51)	35 (49)
Vegetables	14 (18)	22 (30)	27 (38)
Other[1]	15 (19)	20 (27)	30 (42)
Number of food allergies, n (%)			
1 food	15 (19)	9 (12)	12 (17)
2 foods	16 (20)	12 (16)	14 (19)
3 foods	16 (20)	15 (20)	8 (11)
>3 foods	32 (41)	38 (51)	38 (53)
Type of symptoms, n (%)			
Cardiovascular symptoms[2]	28 (35)	31 (58)	44 (61)
Respiratory symptoms[3]	56 (71)	61 (82)	60 (83)
Gastrointestinal symptoms[4]	49 (62)	47 (64)	48 (67)
Skin symptoms[5]	69 (87)	60 (81)	55 (76)
Other[6]	66 (84)	66 (89)	62 (86)

[1] E.g. lupine, kernels and seeds, herbs and spices, meat.
[2] dizziness, feeling your heart beat fast, loss of vision, inability to stand, light headedness, collapse, loss of consciousness / passing out
[3] tightening throat, difficulty swallowing, hoarseness / hoarse voice, difficulty breathing in, shortness of breath, wheezing, cough
[4] nausea, stomach cramps, vomiting, diarrhea
[5] itchy skin, red rash, urticaria, worsening eczema, swelling of the skin
[6] oral allergy, swollen tongue or lips, symptoms of the nose or eyes

Floor and ceiling effects

In children, the CHQ-CF87 showed almost no floor effects because the minimal score (worst HRQL) was seldom reported (Table 3). However, remarkable ceiling effects were seen for the scales role functioning-emotional (RE), role functioning-behaviour (RB) and role functioning-physical (RP) where more than 80% of the children reported the maximal score (best HRQL). A similar pattern was seen in adolescents. In adults, the RAND-36 showed some floor effects (worst HRQL), and pronounced ceiling effects (best HRQL), especially for the scale RE (79%). The disease-specific FAQLQs and domains showed minimal if any floor or ceiling effects, indicating that almost no food allergic patients reported the minimal FAQLQ score (best HRQL) or maximal FAQLQ score (worst HRQL), respectively. This indicates that these questionnaires are potentially longitudinally responsive to the specific concerns of food allergic patients and it underscores the internal validity of these questionnaires.

Table 3. Percentage of floor and ceiling effects of the CHQ-CF87, RAND-36 and FAQLQ-CF, -TF and -AF

	Children			Adolescents			Adults	
	Floor %	Ceiling %		Floor %	Ceiling %		Floor %	Ceiling %
CHQ-CF87			**CHQ-CF87**			**RAND-36**		
PF	0	64.8	PF	0	58.1	PF	0	26.0
RE	1.3	81.0	RE	1.4	73.0	SF	1.4	23.0
RB	0	82.3	RB	0	81.1	RP	19.4	58.3
RP	0	86.1	RP	2.7	85.1	RE	11.1	79.2
BP	0	41.8	BP	1.4	20.3	MH	0	2.8
BE	0	5.1	BE	0	0	VT	0	1.4
MH	0	2.6	MH	0	0	BP	0	37.5
SE	0	6.3	SE	0	0	GH	0	2.8
GH	0	3.8	GH	0	0			
FA	0	31.6	FA	0	24.3			
FC	0	25.3	FC	0	23.0			
FAQLQ-CF	1.3	0	**FAQLQ-TF**	0	1.4	**FAQLQ-AF**	1.4	0
AA	1.3	0	AADR	0	1.4	AADR	2.8	0
RAE	2.5	3.8	RAE	1.4	2.7	RAE	1.4	1.4
EI	5.1	1.3	EI	0	1.4	EI	1.4	1.4
DR	2.5	2.5				FAH	6.9	4.2

Floor effect = percentage of patients with minimal score.
Ceiling effect = percentage of patients with maximal score.
Floor and ceiling of CHQ-CF87 and RAND-36 are score 0 (worst HRQL) and 100 (best HRQL), respectively. Floor and ceiling of the FAQLQ-CF, -TF and -AF are score 1 (best HRQL) and 7 (worst HRQL), respectively.
PF=Physical functioning, RE=Role functioning-emotional, RB=Role functioning-behaviour, RP=Role functioning-physical, BP=Bodily pain, BE=General behaviour, MH=Mental health, SE=Self-esteem, GH=General health, FA=Family activities, FC=Family cohesion, SF=Social functioning, VT=Vitality, AA=Allergen avoidance, RAE=Risk of accidental exposure, EI=Emotional impact, DR=Dietary restrictions, AADR=Allergen avoidance and dietary restrictions, FAH=Food allergy related health

Percentage of agreement

Disease-specific questionnaires as starting point

Table 4 shows the percentage of agreement of the 10% of patients with the worst or best HRQL identified by the disease-specific FAQLQs. For example, of the 10% of children with the worst disease-specific HRQL measured with the FAQLQ-CF, 25% of them also had the worst generic HRQL as measured with the CHQ-CF87 scale physical functioning (PF). The agreement between the 10% of patients with the best disease-specific HRQL and best generic HRQL was generally higher than the agreement between the 10% of patients with the worst disease-specific HRQL and worst generic HRQL.

Table 4. Percentage of agreement of the 10% of patients with the worst[1] or best[2] HRQL identified by the disease-specific questionnaires.

	CHQ-CF87										
	PF	**RE**	**RB**	**RP**	**BP**	**BE**	**MH**	**SE**	**GH**	**FA**	**FC**
FAQLQ-CF											
Worst[1], %	25	38	13	13	13	13	25	50	25	13	0
Best[2], %	63	75	75	88	63	13	13	13	0	38	13
FAQLQ-TF											
Worst[1], %	14	14	14	14	14	29	29	57	14	29	14
Best[2], %	71	100	100	100	43	29	29	43	14	71	43
	RAND-36										
	PF	**SF**	**RP**	**RE**	**MH**	**VT**	**BP**	**GH**			
FAQLQ-AF											
Worst[1], %	14	43	43	43	29	29	14	0			
Best[2], %	14	14	71	71	29	0	14	0			

[1] Worst = the 10% of patients with the highest scores on the FAQLQs, thus the worst HRQL
[2] Best = the 10% of patients with the lowest scores on the FAQLQs, thus the best HRQL
PF=Physical functioning, RE=Role functioning-emotional, RB=Role functioning-behaviour, RP=Role functioning-physical, BP=Bodily pain, BE=General behaviour, MH=Mental health, SE=Self-esteem, GH=General health, FA=Family activities, FC=Family cohesion, SF=Social functioning, VT=Vitality.

Generic questionnaires as starting point

When taking the generic questionnaires as starting point, we found that of the 10% of children with the worst HRQL measured with the CHQ-CF87 scales, 0% (FC) to 44% (RP) of them also had the worst disease-specific HRQL as measured with the FAQLQ-CF. Of the 10% of adolescents with the worst HRQL measured with the CHQ-CF87 scales, 11% (RE) to 57% (SE) of them also had the worst disease-specific HRQL as measured with the FAQLQ-TF. Of the 10% of adults with the worst HRQL measured with the RAND-36 scales, 14% (PF) to 44% (VT) of them also had the worst disease-specific HRQL as measured with

the FAQLQ-AF. However, it was not possible to accurately identify the 10% of patients with the best HRQL for the majority of CHQ-CF87 or RAND-36 scales, because many patients scored the maximal score of 100, which indicates the best generic HRQL (see also Table 3 on ceiling effects).

Table 5. Results of the multivariate regression analysis of the disease-specific and generic HRQL questionnaires.

	FAQLQ-CF	**CHQ-CF87**	
		FA (r=-0.45)	**PF** (r=0.13)
Children			
Explained variance, %[1]	36.1	14.5	n.s.
Intercept	1.24	105.5	n.s.
Mean FAIM	0.74 (p<0.001)	-3.3 (p=0.019)	n.s.
Severity of symptoms	n.s.[2]	n.s.	n.s.
Number of food allergies	n.s.	-2.5 (p=0.0013)	n.s.
	FAQLQ-TF	**CHQ-CF87**	
		FA (r=-0.43)	**RE** (r=-0.15)
Adolescents			
Explained variance, %[1]	30.7	22.1	6.7
Intercept	0.37	96.4	99.3
Mean FAIM	0.61 (p<0.001)	n.s.	n.s.
Severity of symptoms	0.23 (p=0.029)	n.s.	n.s.
Number of food allergies	n.s.	-3.8 (p<0.001)	-2.6 (p=0.015)
	FAQLQ-AF	**RAND-36**	
		MH (r=-0.27)	**BP** (r=0.01)
Adults			
Explained variance, %[1]	62.8	26.2	5.2
Intercept	-0.63	79.9	88.4
Mean FAIM	0.83 (p<0.001)	-8.5 (p<0.001)	n.s.
Severity of symptoms	0.13 (p=0.024)	4.6 (p=0.002)	n.s.
Number of food allergies	0.26 (p=0.003)	n.s.	-3.4 (p=0.030)

[1] based on adjusted R2
[2] n.s. = not significant
FA=Family activities, PF=Physical functioning, RE=Role functioning-emotional, MH=Mental health, BP=Bodily pain.

Generic and disease-specific HRQL explained by patient characteristics

The explained variance in HRQL was higher in the disease-specific questionnaires, ranging from 30.7% for the FAQLQ-TF to 62.8% for the FAQLQ-AF, than in the generic scales (Table 5). Even in the generic scales that correlated the best with the FAQLQs, family activities (FA)

in children and adolescents and mental health (MH) in adults respectively, the explained variance in HRQL was lower than in the disease-specific questionnaires, ranging from 14.5% for FA in children to 26.2% for MH in adults.

In the disease-specific FAQLQs the mean FAIM had the most pronounced association with HRQL (higher score indicates greater impact on HRQL). This was also seen in the generic FA and MH scale, but here the association was negative since a higher score on the generic questionnaires indicates a better HRQL. Interestingly, having more severe symptoms was associated with a better MH score in adults. Type of food allergy, defined as a dichotomous variable peanut allergy versus other food allergies, showed no significant association with HRQL (not shown).

DISCUSSION

In this study we found very high ceiling effects for some scales of the generic questionnaires. No significant floor or ceiling effects were found for the disease-specific FAQLQs. Additionally, we found generally low percentages of agreement between the generic and disease-specific questionnaires in the identification of the same food allergic patients with the best or worst HRQL. Only patients with the best disease-specific HRQL also tended to score the best generic HRQL. Finally, the explained variance in HRQL by patient characteristics was higher for the disease-specific questionnaires than for the generic scales.

One of the disadvantages of generic questionnaires is that they are by design comprehensive, so they may not focus adequately on problems specific to a particular disease. In the current study, we found very high ceiling effects for some scales of the generic questionnaires, which indicate that a substantial part of the food allergic patients reported no problems in these areas. Thus, some areas measured by generic questionnaires are irrelevant to food allergy. Generic questionnaires may therefore be not useful for measuring disease-specific clinically important impairments in HRQL or HRQL differences over time in food allergic patients. In contrast, no significant floor or ceiling effects were observed for the disease-specific FAQLQs. This indicates that these questionnaires are potentially longitudinally responsive to the specific concerns of food allergic patients and it underscores the internal validity of these questionnaires.

Furthermore, we found that patients with the best disease-specific HRQL also tended to score the best generic HRQL (high percentage of agreement). However, patients with the worst disease-specific HRQL do not always have the worst generic HRQL (low percentage of agreement). A possible explanation is that coping strategy differences may modify scores in severely affected patients, while this is not the case in relatively unaffected patients. The same result was found when comparing the RAND-36 with disease-specific questionnaires in patients with diabetes mellitus type 1[26]. Again, this

low percentage of agreement suggests that the disease-specific questionnaires are more capable of capturing the specific aspects that impair HRQL in a food allergy than the broader generic questionnaires. This implies that if one wishes to identify or select food allergic patients with the worst HRQL, the type of questionnaire will influence which patients are identified[26].

When looking at the results of the regression analyses, we found that the FAIM had a more pronounced association with HRQL than the clinical patient characteristics such as severity of symptoms and number of food allergies. Even the type of food allergy showed no association with HRQL. This underlines our premise published earlier that objective parameters in food allergy are not as closely linked to HRQL of food allergic patients as the FAIM scores[6], and that these objective measures are thus less appropriate as an independent measure for the development of HRQL instruments in food allergy[20].

Although generic HRQL questionnaires may be not as sensitive as disease-specific questionnaires, the advantages of generic questionnaires is that they can be used to compare patients with the general population and that they can be used to compare different diseases[27]. In a previous study we showed that, in general, food allergic patients reported poorer HRQL than the general population. Additionally, it was shown that generic HRQL was more impaired in food allergic patients than in patients with diabetes mellitus type I, but less impaired than in patients with asthma, irritable bowel syndrome and rheumatoid arthritis[28]. Therefore, the effect of an intervention in food allergy may be best evaluated by using both generic and disease-specific HRQL questionnaires, as the FAQLQs may be more sensitive to detect disease-specific clinically important impairments in HRQL or HRQL differences over time, whereas generic HRQL questionnaires allow for comparison between different diseases which may be relevant in comparative economic analysis[29].

In conclusion, the very high ceiling effects that were found for some generic scales may indicate that generic HRQL questionnaires are not sufficiently responsive in food allergy to measure disease-specific but potentially clinically important impairments in HRQL or HRQL differences over time. This finding was further supported by the low agreement between the generic and disease-specific questionnaires to identify food allergic patients with the best or worst HRQL, as well as the higher explained variance in HRQL by characteristics of food allergic patients in the disease-specific questionnaires than in the generic scales. Therefore for measuring disease-specific clinically important impairments in HRQL or HRQL differences over time in food allergic patients, it may be preferable to use disease-specific HRQL questionnaires. However, generic HRQL questionnaire are indispensable for the comparison between different diseases and are thus complementary.

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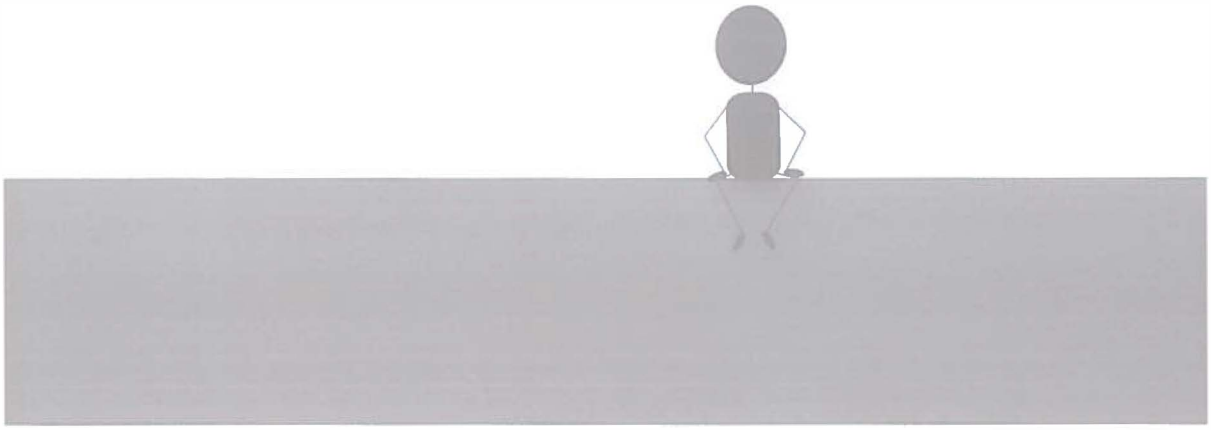
REFERENCE LIST

1. Munoz-Furlong A . Living with food allergies: not as easy as you might think. FDA Consum 2001; 35:40.
2. Munoz-Furlong A. Daily coping strategies for patients and their families. Pediatrics 2003; 111:1654-61.
3. Bock SA, Munoz-Furlong A, Sampson HA. Further fatalities caused by anaphylactic reactions to food, 2001-2006. J Allergy Clin Immunol 2007; 119:1016-8.
4. Marklund B, Ahlstedt S, Nordstrom G. Food hypersensitivity and quality of life. Curr Opin Allergy Clin Immunol 2007; 7:279-87.
5. Guyatt GH, Feeny DH, Patrick DL. Measuring health-related quality of life. Ann Intern Med 1993; 118:622-9.
6. Flokstra-de Blok BM, Dubois AE. Quality of life in food allergy: valid scales for children and adults. Curr Opin Allergy Clin Immunol 2009; 9:214-21.
7. Avery NJ, King RM, Knight S, Hourihane JO. Assessment of quality of life in children with peanut allergy. Pediatr Allergy Immunol 2003; 14:378-82.
8. Bollinger ME, Dahlquist LM, Mudd K, Sonntag C, Dillinger L, McKenna K. The impact of food allergy on the daily activities of children and their families. Ann Allergy Asthma Immunol 2006; 96:415-21.
9. Cohen BL, Noone S, Munoz-Furlong A, Sicherer SH. Development of a questionnaire to measure quality of life in families with a child with food allergy. J Allergy Clin Immunol 2004; 114:1159-63.
10. Lebovidge JS, Stone KD, Twarog FJ, et al. Development of a preliminary questionnaire to assess parental response to children's food allergies. Ann Allergy Asthma Immunol 2006; 96:472-7.
11. Marklund B, Ahlstedt S, Nordstrom G. Health-related quality of life among adolescents with allergy-like conditions - with emphasis on food hypersensitivity. Health Qual Life Outcomes 2004; 2:65.
12. Marklund B, Ahlstedt S, Nordstrom G. Health-related quality of life in food hypersensitive schoolchildren and their families: parents' perceptions. Health Qual Life Outcomes 2006; 4:48.
13. Ostblom E, Egmar AC, Gardulf A, Lilja G, Wickman M. The impact of food hypersensitivity reported in 9-year-old children by their parents on health-related quality of life. Allergy 2008; 63:211-8.
14. Primeau MN, Kagan R, Joseph L, et al. The psychological burden of peanut allergy as perceived by adults with peanut allergy and the parents of peanut-allergic children. Clin Exp Allergy 2000; 30:1135-43.
15. Sicherer SH, Noone SA, Munoz-Furlong A. The impact of childhood food allergy on quality of life. Ann Allergy Asthma Immunol 2001; 87:461-4.
16. DunnGalvin A, de BlokFlokstra BM, Burks AW, Dubois AE, Hourihane JO. Food allergy QoL questionnaire for children aged 0-12 years: content, construct, and cross-cultural validity. Clin Exp Allergy 2008; 38:977-86.
17. Flokstra-de Blok BM, DunnGalvin A, Vlieg-Boerstra BJ, et al. Development and validation of the self-administered Food Allergy Quality of Life Questionnaire for adolescents. J Allergy Clin Immunol 2008; 122:139-44.
18. Flokstra-de Blok BMJ, van der Meulen GN, DunnGalvin A, et al. Development and validation of the Food Allergy Quality of Life Questionnaire-Adult Form (FAQLQ-AF). Allergy 2009; 64:1209-17.
19. Flokstra-de Blok BM, DunnGalvin A, Vlieg-Boerstra BJ, et al. Development and validation of a self-administered Food Allergy Quality of Life Questionnaire for children. Clin Exp Allergy 2009; 39:127-37.
20. van der Velde JL, Flokstra-de Blok BM, Vlieg-Boerstra BJ, et al. Development, validity and reliability of the Food Allergy Independent Measure (FAIM). Allergy 2010; 65:630–5
21. Landgraf JM, Abetz L, Ware JE. Child Health Questionnaire (CHQ): a user's manual. 2nd ed. Boston: HealthAct; 1999.
22. Raat H, Landgraf JM, Bonsel GJ, Gemke RJ, Essink-Bot ML. Reliability and validity of the child health questionnaire-child form (CHQ-CF87) in a Dutch adolescent population. Qual Life Res 2002; 11:575-81.
23. van der Zee KI, Sanderman R. Het meten van de algemene gezondheidstoestand met de RAND-36: een handleiding. Groningen: Noordelijk Centrum voor Gezondheidsvraagstukken; 1993.
24. Ware JE, Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 1992; 30:473-83.
25. van der Velde JL, Flokstra-de Blok BM, Vlieg-Boerstra BJ, et al. Test-retest reliability of the Food Allergy Quality of Life Questionnaires (FAQLQ) for children, adolescents and adults. Qual Life Res 2009; 18:245-51.
26. Hart HE, Redekop WK, Bilo HJ, Meyboom-de Jong B, Berg M. Health related quality of life in patients with type I diabetes mellitus: generic & disease-specific measurement. Indian J Med Res 2007; 125:203-16.

27. Testa MA, Simonson DC. Assesment of quality-of-life outcomes. N Engl J Med 1996; 334:835-40.

28. Flokstra-de Blok BMJ, Dubois AEJ, Vlieg-Boersta BJ, et al. Health-related quality of life of food allergic patients: Comparison with other diseases and the general population. Allergy 2010; *65*:238–44.

29. Terreehorst I, Duivenvoorden HJ, Tempels-Pavlica Z, et al. Comparison of a generic and a rhinitis-specific quality-of-life (QOL) instrument in patients with house dust mite allergy: relationship between the SF-36 and Rhinitis QOL Questionnaire. Clin Exp Allergy 2004; 34:1673-7.



Chapter 3

Test-retest reliability of the Food Allergy Quality of Life Questionnaires (FAQLQs) for children, adolescents and adults

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ABSTRACT

Objective: The self-administered Food Allergy Quality of Life Questionnaire-Child Form (FAQLQ-CF), -Teenager Form (FAQLQ-TF) and -Adult Form (FAQLQ-AF) were recently developed within EuroPrevall, a multi-centred study of food allergy in Europe. The primary aim of this study was to evaluate the test-retest reliability of the FAQLQ-CF, -TF and -AF.

Methods: One-hundred-and-one Dutch patients (31 children, 34 adolescents and 36 adults) completed the FAQLQ twice with a 10-14 day interval. The intraclass correlation coefficient (ICC), Lin's concordance correlation coefficient (CCC) and Bland-Altman plots were used to assess test-retest reliability.

Results: Test-retest reliability was excellent with ICCs and CCCs above 0.907, 0.975 and 0.951 for the FAQLQ-CF, -TF and -AF, respectively. Bland Altman plots showed that the mean differences of the test and re-test were all close to zero for the FAQLQs.

Conclusions: The FAQLQs are reliable over a short time interval. The FAQLQs are not only promising tools for group comparison studies, but also for monitoring individual patients.

INTRODUCTION

Food allergy affects almost 4 % of the general population in westernized countries[1] and it is the primary cause of anaphylaxis presenting to emergency departments[2]. The only proven therapy is careful avoidance of the causal food(s) and provision of medication for emergency treatment[3]. Consequently, patients often fear an allergic reaction and are continuously faced with dietary and social restrictions in their daily lives, which can have a negative impact on quality of life[4-11].

To measure Health-Related Quality of Life (HRQL), disease-specific questionnaires are significantly more sensitive than generic ones and they are important for estimating the general burden of food allergy as well as measuring the response to interventions or future treatments. However, generic HRQL instruments allow comparison of the burden of disease between patient populations with different diseases[12]. Recently, as part of the EuroPrevall project, the first self-administered HRQL questionnaires specific for food allergy have been developed and validated; the Food Allergy Quality of Life Questionnaire-Child Form, -Teenager Form and -Adult Form (FAQLQ-CF, -TF, -AF). The FAQLQs showed good validity, internal consistency and discriminative abilities[13-16], but test-retest reliability was not extensively investigated.

Reliability measures are important to ensure that what the questionnaire is measuring is dependable and repeatable[12] and allow sample sizes to be determined for clinical trials[17]. The aim of this study was therefore to assess the test-retest reliability of the self-administered FAQLQ-CF, -TF and -AF.

METHODS

Patients

We contacted Dutch children (8-12 years), adolescents (13-17 years) and adults (≥18 years) with food allergy, who were recruited from our clinic or by advertisement. We included patients with the most prevalent food allergies.

Questionnaires

The FAQLQ-CF contains 24 items and 4 domains, the FAQLQ-TF contains 23 items and 3 domains and the FAQLQ-AF contains 29 items and 4 domains[13-15]. Following the guidelines of other established RHQL studies, each item is scored on a scale ranging from 1 (minimal impairment in HRQL) to 7 (maximal impairment in HRQL)[18-19]. The total FAQLQ score is the sum of all the items divided by the number of items.

Procedures

We sent the FAQLQs by mail to be completed at home. Regarding the FAQLQ-CF, parents were instructed that they were allowed to explain a question when needed,

but they were not allowed to tell the child which answer to give. All patients who completed the first questionnaires (test) received the second questionnaires (re-test) 10-14 days after completion of the first. Patients who did not respond in time were excluded from the study[20,21] as well as patients who reported a clinically important change in disease between the measurements or within two months before the study. We defined a clinically important change in disease which may influence HRQL as a food allergic reaction of grade 3 or 4 according to the Mueller classification[22]. The study was approved by the local medical ethics review commission (METc 2005/051).

Statistical Analysis

Data were analysed using SPSS software for Windows (Version 14.0). To investigate test-retest reliability of the FAQLQs we used the intraclass correlation coefficient (ICC), using a one-way ANOVA[20,21,23]. Values should be above 0.70 for group comparison studies and above 0.90-0.95 for individual measurements over time[24].

As a second measure of test-retest reliability we calculated the Lin's concordance correlation coefficient (CCC). The different components of the CCC (Pearson correlation coefficient [measure of precision], location shift and scale shift [measures of accuracy]), were calculated. We plotted the first measurement against the second measurement and we used major axis analyses to calculate the best fitting line[25].

Visual assessment of test-retest agreement was obtained by use of Bland-Altman plots[26]. Differences between the first and the second measurement were plotted against the mean of the first and the second measurement. Limits of agreement (mean difference +/- 1.96*SD of the difference) were calculated, which reflect the interval within which about 95% of the differences between the two measurements should lie[27,28]. A regression coefficient (*r*) was calculated to estimate a relationship between the difference and the mean[26].

Table 1. Patient Recruitment

Patients	Children	Adolescents	Adults	Total
Contacted patients, n	48	51	49	148
Returned 1st questionnaire, n	41	47	43	131
Returned 2nd questionnaire, n	38	38	38	114
Excluded patients[1], n	7	4	2	13
Analysed patients, n	**31**	**34**	**36**	**101**

[1] Seven patients (3 children, 3 adolescents, 1 adult) were excluded, because they completed the second questionnaire more than 14 days after completion of the first. One child and 1 adult were excluded because of a grade 3 or 4 allergic reaction between the first and second measurement. One child was excluded because she was aged under 8 years. Two children and 1 adolescent were excluded because they experienced their most severe reaction ever within 2 months before the first measurement.

RESULTS

Patients

We contacted 148 patients, of which 131 patients completed and returned the first questionnaire and 114 responded to the second questionnaire. This resulted in an overall response rate of 77%. A few patients were excluded, resulting in 101 patients that were eligible for analysing test-retest reliability (Table 1). The descriptive characteristics of the participants are shown in table 2. Mean duration between the first and second measurement was 11 days for all three age groups.

Table 2. Demographics and Clinical Characteristics

	Children (n= 31)		**Adolescents** (n= 34)		**Adults** (n= 36)	
Mean age, years (SD)	10.6	(1.5)	15.0	(1.5)	37.3	(14.5)
Gender, n (%)						
Male	17	(55)	18	(53)	7	(19)
Female	14	(45)	16	(47)	29	(81)
Type food allergy, n (%)						
Peanut	25	(81)	30	(88)	25	(69)
Nut	17	(55)	28	(82)	25	(69)
Milk	15	(48)	15	(44)	15	(42)
Egg	14	(45)	16	(47)	7	(19)
Wheat	5	(16)	4	(12)	7	(19)
Soy	9	(29)	13	(38)	8	(22)
Sesame	7	(23)	9	(26)	6	(17)
Fish	2	(6)	5	(15)	9	(25)
Shell fish	6	(19)	8	(24)	12	(33)
Celery	0	(0)	4	(12)	8	(22)
Fruit	14	(45)	13	(38)	26	(72)
Vegetables	6	(19)	6	(18)	10	(28)
Others	25	(81)	24	(71)	13	(36)
Number of food allergies, n (%)						
1 food	6	(19)	3	(9)	1	(3)
2 foods	4	(13)	4	(12)	3	(8)
3 foods	4	(13)	8	(24)	10	(28)
> 3 foods	17	(55)	19	(56)	22	(61)
Severity of Symptoms						
Mueller Classification, n (%)						
Grade 1	6	(19)	2	(6)	3	(8)
Grade 2	2	(6)	3	(9)	3	(8)
Grade 3	17	(55)	18	(53)	13	(36)
Grade 4	6	(19)	9	(26)	17	(47)
Other[1]	0	(0)	2	(6)	0	(0)
Most severe reaction,						
How many years ago? (SD)	4.6	(3.6)	7.1	(5.4)	5.2	(7.5)
Diagnosed by, n (%)						
Specialist[2]	26	(83)	25	(74)	25	(69)
Dietician	0	(0)	1	(3)	0	(0)
General Practitioner	4	(13)	6	(18)	3	(8)
Patient	0	(0)	0	(0)	4	(11)
Parents	0	(0)	2	(6)	1	(3)

[1] Other food allergy types not specified in the Mueller Classification, for example the Oral Allergy Syndrome.
[2] Allergist, Dermatologist or Paediatrician

Analysis of FAQLQs

ICCs were ≥ 0.900 for the FAQLQs and CCCs were comparably high. Location shift and scale shift, should all be considered minimal according to Lin's examples[29]. Pearson correlation should be considered moderate in the FAQLQ-CF and good in the FAQLQ-TF and -AF (Table 3). Comparable results were found for the individual domains of the FAQLQs (data not shown).

Table 3. Reliability and Agreement measures of the FAQLQs

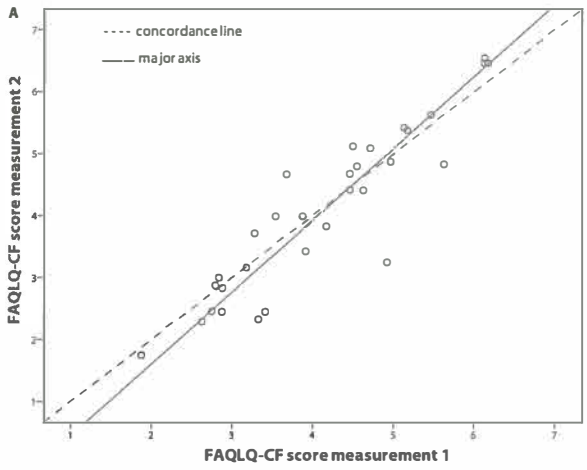
	FAQLQ-CF	FAQLQ-TF	FAQLQ-AF
M1 (SD1)	4.13 (1.15)	4.37 (1.20)	4.49 (1.44)
M2 (SD2)	4.08 (1.34)	4.42 (1.29)	4.34 (1.59)
Mean of both scores, M1+M2 (SD)	4.11 (1.22)	4.40 (1.24)	4.41 (1.50)
Mean difference, M1-M2 (SD)	0.045 (0.537)	-0.051 (0.274)	0.147 (0.451)
Limits of agreement (1.96 SD)	-1.008 to 1.097	-0.588 to 0.486	-0.737 to 1.031
ICC one-way (95 % CI)	0.910 (0.823-0.955)	0.976 (0.952-0.988)	0.952 (0.909-0.975)
Error variance	0.147	0.038	0.102
CCC (95% CI)	0.907 (0.847-0.967)	0.975 (0.959-0.991)	0.951 (0.921-0.981)
Scale shift	1.162	1.077	1.104
Location shift	0.036	-0.041	0.097
Pearson	0.918	0.978	0.960
Kendall's tau-b	0.759	0.888	0.780

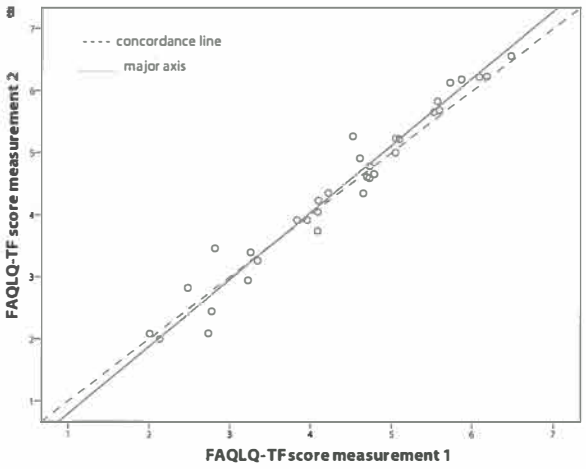
M1 = Total FAQLQ score measurement 1
M2 = Total FAQLQ score measurement 2
SD = Standard deviation
CI = Confidence interval
Limits of agreement: Mean difference +/- 1.96 SD of the mean difference
ICC = Intraclass correlation coefficient
CCC = Concordance correlation coefficient
Scale shift (SD2/SD1)
Location shift: (M1–M2)

$$\frac{SD1 + SD2}{\sqrt{SD1 \times SD2}}$$

Figure 1 illustrates the correlation between the first and second measurement. Major axis analysis revealed no significant differences of the slope and intercept of the best fitting line from the concordance line for the FAQLQ-CF and -TF. For the FAQLQ-AF there were significant but modest differences of the slope (1.10, $p = 0.046$) and the intercept (-0.612, $p = 0.019$) of the best fitting line from the concordance line. The slope and intercept of the best fitting line of the FAQLQ-CF, -TF and -AF did not differ significantly from each other.

Figure 1. FAQLQ score of the first measurement against FAQLQ score of the second measurement with 45° line through the origin in (A) children, (B) adolescents and (C) adults.





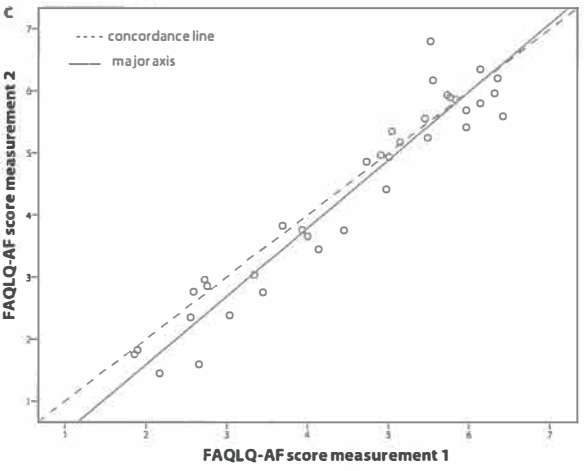
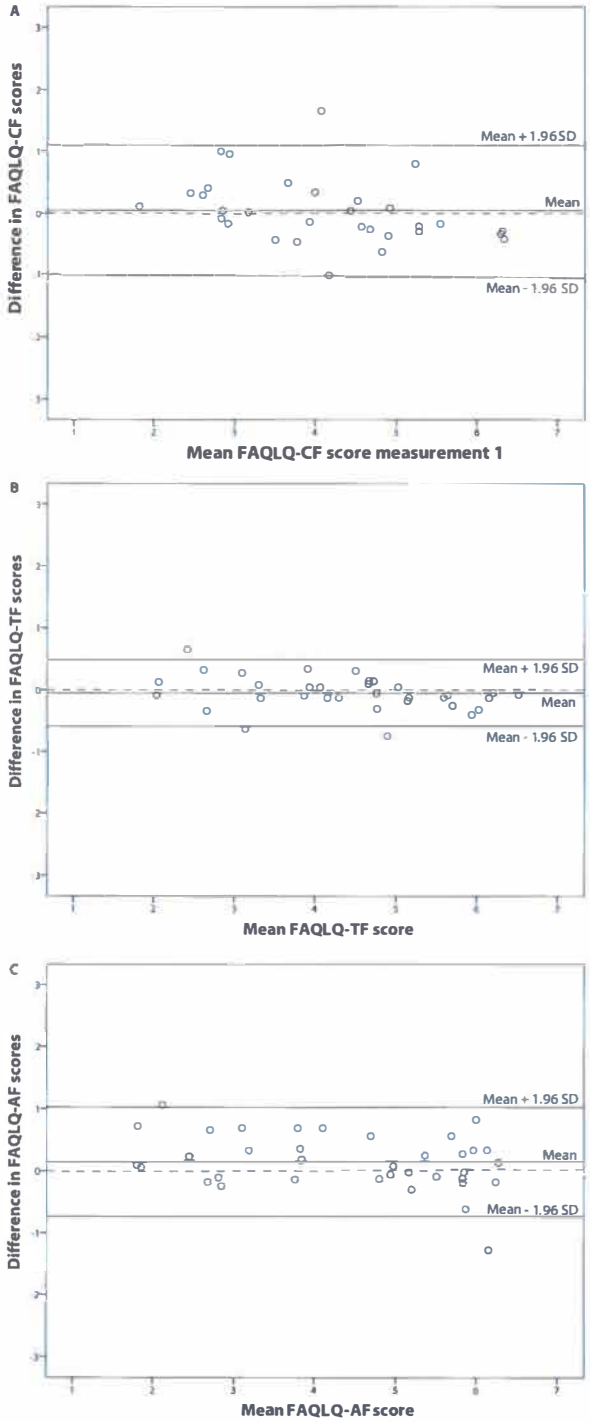


Figure 2. Bland-Altman plots for the FAQLQs in (A) children, (B) adolescents and (C) adults. The mean of both measurements are plotted against the difference of both measurements (calculated as first measurement minus second measurement)



The Bland-Altman plots are shown in figure 2. About 95% of the differences lie within the 1.96 SD limits of agreement. There was no significant correlation between the mean of both scores and the differences of both scores for the FAQLQ-CF and -TF. There was a significant but modest correlation between the mean of both scores and the differences of both scores for the FAQLQ-AF ($r = -0.334$; $p = 0.046$). No significant systematic bias was observed, which means that mean differences of both scores were all close to zero. The limits of agreement are most narrow for FAQLQ-TF and wider for FAQLQ-CF and -AF.

DISCUSSION

This article describes the evaluation of the test-retest reliability of the recently developed self-administered FAQLQ-CF, -TF and -AF. Overall, reliability was considered to be excellent for the FAQLQs as measured with the ICC and CCC. Additionally, Bland-Altman plots showed that mean differences were all close to zero, supporting the high reliability of the FAQLQs.

In this study we used ICCs calculated by a one-way ANOVA, CCCs and Bland-Altman plots to assess test-retest reliability. However, different methods can be used to assess test-retest reliability and there is much discussion in literature on the best way to do this[20]. A disadvantage of the ICC is that if patient groups are very homogeneous, the ICC tends to be low, because the ICC compares variance among patients to total variance. If patient groups are very heterogeneous, the ICC tends to be high. Thus, the ICC would only generalize to similar populations. Additionally, the one-way ICC does not take into account the order in which observations were taken[29]. Therefore, the CCC is a useful additional measure. The CCC takes into account not only mean differences between the first and second measurement, such as ICCs calculated by a one-way ANOVA, but also takes into account variance differences between the first and second measurement by reducing the magnitude of the resulting test-retest reliability estimate. In addition, the CCC is a better tool to distinguish between bias and imprecision[20,29]. There can be large differences in ICC and CCC scores, especially in studies with heterogeneous groups. The similar scores we found in our study reflect that both coefficients worked very well in this population and that results can be generalized to other groups. Bland-Altman plots are very illustrative in assessing test-retest agreement. They were useful to identify some extreme and outlying differences, to analyse the magnitude of the measurement error, which was small, and to visualize a possible relationship between the difference and the mean of both scores[26].

This study may also have some limitations. Firstly, the sample sizes were relatively small. However, we found that the reliability of the questionnaires was very high, which indicates that the sample sizes were adequate and that a greater number of patients would probably not have influenced the outcomes. Another limitation may be that the majority of adults in this study was female. However, we did not find significant differences in the

test-retest reliably outcomes between men and women (data not shown). Therefore, we think that the imbalance between men and women did not influence the generalisability of the results of the FAQLQ-AF. Finally, the significant correlation between the first and second measurement of the FAQLQ-AF (figure 1C) and between the mean of both scores and the differences of both scores of the FAQLQ-AF (figure 2C) was an unexpected finding. We think this correlation might be due to an outlier. This assumption was supported by a re-analysis excluding this outlier, which showed that the correlation was no longer significant.

In summary, the FAQLQs showed excellent reliability and are thus promising measures in evaluative studies in patients with food allergy, but also in monitoring individual patients. The high test-retest reliability supports the value of the FAQLQs for clinical trials with relatively small sample sizes. We recommend the use of the FAQLQs in clinical trials of current management strategies of food allergy and they may also be useful when new treatments become available. Currently, the longitudinal validity of the FAQLQs and the validity of several other European language versions of the FAQLQs are being investigated.

ACKNOWLEDGEMENTS

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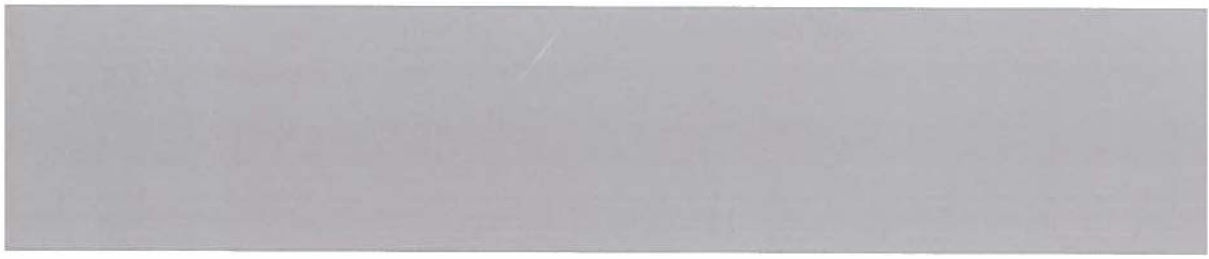
REFERENCE LIST

1. Osterballe M, Hansen TK, Mortz CG, Host A, Bindslev-Jensen C. The prevalence of food hypersensitivity in an unselected population of children and adults. Pediatr Allergy Immunol 2005; 16:567-73.
2. Sampson HA. Food-induced anaphylaxis. Novartis.Found.Symp 2004; 257:161-71.
3. Sampson HA. Update on food allergy. J Allergy Clin Immunol 2004; 113:805-19.
4. Primeau MN, Kagan R, Joseph L et al. The psychological burden of peanut allergy as perceived by adults with peanut allergy and the parents of peanut-allergic children. Clin Exp Allergy 2000; 30:1135-43.
5. Sicherer SH, Noone SA, Munoz-Furlong A. The impact of childhood food allergy on quality of life. Ann Allergy Asthma Immunol 2001; 87:461-4.
6. Avery NJ, King RM, Knight S, Hourihane JO. Assessment of quality of life in children with peanut allergy. Pediatr Allergy Immunol 2003; 14:378-82.
7. Cohen BL, Noone S, Munoz-Furlong A, Sicherer SH. Development of a questionnaire to measure quality of life in families with a child with food allergy. J Allergy Clin Immunol 2004; 114:1159-63.
8. Marklund B, Ahlstedt S, Nordstrom G. Health-related quality of life among adolescents with allergy-like conditions - with emphasis on food hypersensitivity. Health Qual Life Outcomes 2004; 2:65.
9. Marklund B, Ahlstedt S, Nordstrom G. Health-related quality of life in food hypersensitive schoolchildren and their families: parents' perceptions. Health Qual Life Outcomes 2006; 4:48.
10. Lebovidge JS, Stone KD, Twarog FJ et al. Development of a preliminary questionnaire to assess parental response to children's food allergies. Ann Allergy Asthma Immunol 2006; 96:472-7.
11. Bollinger ME, Dahlquist LM, Mudd K et al. The impact of food allergy on the daily activities of children and their families. Ann Allergy Asthma Immunol 2006; 96:415-21.
12. Testa MA, Simonson DC. Assesment of quality-of-life outcomes. N Engl J Med 1996; 334:835-40.
13. Flokstra-de Blok BM, DunnGalvin A, Vlieg-Boerstra BJ et al. Development and validation of a self-administered Food Allergy Quality of Life Questionnaire for children. Clin Exp Allergy 2009; 39:127-37.
14. Flokstra-de Blok BM, DunnGalvin A, Vlieg-Boerstra BJ et al. Development and validation of the self-administered Food Allergy Quality of Life Questionnaire for adolescents. J Allergy Clin Immunol 2008; 122:139-44.
15. Flokstra-de Blok BMJ, van der Meulen GN, DunnGalvin A et al. Development and validation of the Food Allergy Quality of Life Questionnaire-Adult Form (FAQLQ-AF). Allergy 2009; 64:1209-17.
16. DunnGalvin A, de BlokFlokstra BM, Burks AW, Dubois AE, Hourihane JO. Food allergy QoL questionnaire for children aged 0-12 years: content, construct, and cross-cultural validity. Clin Exp Allergy 2008; 38:977-86.
17. Guyatt G, Walter S, Norman G. Measuring change over time: assessing the usefulness of evaluative instruments. J Chronic Dis 1987; 40:171-8.
18. Oude Elberink JN, de Monchy JG, Golden DB et al. Development and validation of a health-related quality-of-life questionnaire in patients with yellow jacket allergy. J Allergy Clin Immunol 2002; 109:162-70.
19. Juniper EF, Guyatt GH, Jaeschke R. How to develop and validate a new health-related quality of life instrument. In: Spilker B, ed. Quality of life and pharmacoeconomics in clinical trials. Philadelphia: Lippincott-Raven Publishers 1996; 49-56.
20. Schuck P. Assessing reproducibility for interval data in health-related quality of life questionnaires: which coefficient should be used? Qual Life Res 2004; 13:571-86.
21. Deyo RA, Diehr P, Patrick DL. Reproducibility and responsiveness of health status measures. Statistics and strategies for evaluation. Control Clin Trials 1991; 12:142S-158S.
22. Mueller HL. Diagnosis and treatment of insect sensitivity. J Asthma Res 1966; 3:331-3.
23. Terwee CB, Gerding MN, Dekker FW et al. Test-retest reliability of the GO-QOL: a disease-specific quality of life questionnaire for patients with Graves' ophthalmopathy. J Clin Epidemiol 1999; 52:875-84.
24. Assessing health status and quality-of-life instruments: attributes and review criteria. Qual Life Res 2002; 11:193-205.
25. Warton DI, Wright IJ, Falster DS, Westoby M. Bivariate line-fitting methods for allometry. Biol Rev Camb Philos Soc 2006; 81:259-91.
26. Bland JM, Altman DG. Measuring agreement in method comparison studies. Stat Methods Med Res 1999; 8:135-60.

27. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. Lancet 1986; 1:307-10.
28. Bland JM, Altman DG. Measurement error and correlation coefficients. BMJ 1996; 313:41-2.
29. Lin LI. A concordance correlation coefficient to evaluate reproducibility. Biometrics 1989; 45:255-68.



Chapter 4

Development, validity and reliability of the Food Allergy Independent Measure (FAIM)

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ABSTRACT

Objective: The Food Allergy Quality of Life Questionnaire-Child Form, -Teenager Form and -Adult Form (FAQLQ-CF, -TF and -AF) have recently been developed. In order to measure construct validity in the FAQLQs, a suitable independent measure was needed with which FAQLQ scores could be correlated. However, in food allergy, no appropriate independent measure existed, which could be used for this purpose. The aim of this study was to describe the development of a Food Allergy Independent Measure Child-Form, -Teenager Form and -Adult Form (FAIM-CF, -TF and -AF) and to assess their validity and reliability.

Methods: The FAIMs were developed using previously established methodology to capture the patients' expectation of outcome (EO). Face validity was determined by expert opinion. FAIM questions showing no correlation to any potential items in the FAQLQs were considered irrelevant and eliminated. In order to measure test-retest reliability, one-hundred-and-one patients were included and completed the FAIM twice with a 10-14 day interval. The intraclass correlation coefficient (ICC), Lin's concordance correlation coefficient (CCC) and Bland-Altman plots were used to assess test-retest reliability.

Results: Six FAIM questions were developed and considered relevant for the FAIM-CF and -AF and five questions were relevant for the FAIM-TF. The FAIMs showed good reliability with ICCs and CCCs above 0.70 and with mean differences all close to zero.

Conclusions: Food allergy independent measures were developed for children, adolescents and adults and were shown to be valid, relevant and reliable. This supports the suitability of the FAIMs for evaluating construct validity.

INTRODUCTION

In Health Related Quality of Life (HRQL) research, construct validity is the only approach possible to establish validity[1]. Construct validity refers to whether the questionnaire is measuring what it is supposed to measure and can be assessed by correlating a new questionnaire with an independent measure, which reflects disease severity.

In order to measure construct validity in the recently developed Food Allergy Quality of Life Questionnaire-Child Form, -Teenager Form and -Adult Form (FAQLQ-CF, -TF and -AF)[2-4], we needed to demonstrate that the FAQLQs were measuring only that part of HRQL affected by food allergy and not general quality of life aspects. However, in food allergy no appropriate independent measure existed, which could be used for this purpose. Therefore, a Food Allergy Independent Measure-Child Form, -Teenager Form and -Adult Form (FAIM-CF, -TF and -AF) were developed. This study describes the development, validity and reliability of the FAIMs.

METHODS

Development

Development of a Dutch independent measure was carried out using Expectation of Outcome (EO) questions, previously described by Oude Elberink[5,6]. The EO questions capture the perceived expectation of patients of the chance of accidental exposure and the perception of what will happen following accidental exposure. This is likely to be the source of quality of life differences in anaphylactic disorders and is therefore an appropriate independent measure[6]. Each question was scored on a seven-point scale. A consultant for sick children, psychologist and a linguist reviewed the FAIMs for clarity and ease of use.

Validity and relevance

Face validity was determined by expert opinion. Three experts participated in and agreed on the validity of the possible FAIM questions. FAIM questions were considered valid if they addressed aspects of food allergy outcomes that patients were likely to perceive as determining the severity of their condition. Questions showing no correlation to any potential FAQLQ item were not considered relevant and therefore eliminated.

Reliability

Patients and procedures

Dutch children (8-12 years), adolescents (13-17 years) and adults (≥18 years) with food allergy were recruited from our clinic or by advertisement from January 2007 to May 2007.

Figure 1. The FAIM-CF (A) and the FAIM-TF and -AF (B)

A. **The Food Allergy Independent Measure – Child Form (8-12 years)**

The following four questions are about the chance that you think you have of something happening to you because of your food allergy. Choose one of the answers. This is followed by two more questions about your food allergy. Answer every question by putting an 'x' in the box next to the proper answer.

0	1	2	3	4	5	6
never (0% chance)	very small chance	small chance	fair chance	big chance	very big chance	always (100% chance)

How big do you think the chance is that you ...		0	1	2	3	4	5	6
EO1.	will accidentally eat something to which you are allergic?	☐	☐	☐	☐	☐	☐	☐
EO2.	will have a severe reaction if you accidentally eat something to which you are allergic?	☐	☐	☐	☐	☐	☐	☐
EO3.	will die if you accidentally eat something to which you are allergic?	☐	☐	☐	☐	☐	☐	☐
EO4.	Can not do the right things for your allergic reaction should you accidentally eat something to which you are allergic	☐	☐	☐	☐	☐	☐	☐

IM1 How many foods are you unable to eat because of your food allergy?	**IM2** Everyone does things with other people, such as; playing with friends, going to a birthday party, visiting, staying over with someone for a meal or eating out. **How much does your food allergy affect things you do with others?**
☐ almost none	☐ so little I don't actually notice it
☐ very few	☐ very little
☐ a few	☐ a little
☐ some	☐ moderately
☐ many	☐ a good deal
☐ very many	☐ a great deal
☐ almost all	☐ a very great deal

B. **The Food Allergy Independent Measure-Teenager Form (13-17 years) and –Adult Form.**

The following four questions are about the chance that you think you have of something happening to you because of your food allergy. Choose one of the answers provided. This is followed by two questions about your food allergy. Answer every question by putting an 'x' in the box next to the appropriate answer.

0	1	2	3	4	5	6
never (0% chance)	very small chance	small chance	fair chance	great chance	very great chance	always (100% chance)

How great do you think the chance is that you ...		0	1	2	3	4	5	6
EO1.	will accidentally eat something to which you are allergic?	☐	☐	☐	☐	☐	☐	☐
EO2.	will have a severe reaction if you accidentally eat something to which you are allergic?	☐	☐	☐	☐	☐	☐	☐
EO3.[1]	will die if you accidentally eat something to which you are allergic?	☐	☐	☐	☐	☐	☐	☐
EO4.	can not effectively deal with an allergic reaction should you accidentally eat something to which you are allergic	☐	☐	☐	☐	☐	☐	☐

IM1 How many products must you avoid because of your food allergy?	**IM2** How great is the impact of your food allergy on your social life?
☐ almost none	☐ negligibly small
☐ very few	☐ very small
☐ a few	☐ small
☐ some	☐ moderate
☐ many	☐ great
☐ very many	☐ very great
☐ almost all	☐ extremely great

[1] EO question 3 was not considered to be an appropriate Independent measure questionnaire for food allergy in adolescents.

Patients with the most prevalent food allergies were included. The FAIMs were sent by mail to be completed at home. Participation was completely voluntary. Regarding the FAIM-CF, parents were instructed that they were allowed to explain a question when needed, but they were not allowed to tell the child which answer to give. All patients who completed the first questionnaires (test) received the second questionnaires (re-test) 10-14 days after completion of the first. Patients who did not respond within 14 days were excluded from the study as well as patients who reported a clinically important change in health state (defined as a food allergic reaction of grade 3 or 4 according to the Mueller classification[7]) between the measurements or within two months before the study. This study ran in parallel with the test-retest reliability study of the FAQLQs[8]. The study was approved by the local medical ethics review commission (METc 2005/051).

Statistical Analysis

Data were analyzed using SPSS software for Windows (Version 14.0). The intraclass correlation coefficient (ICC), using a one-way ANOVA[9], and Lin's concordance correlation coefficient (CCC)[10] were calculated to investigate test-retest reliability. ICCs and CCCs should be above 0.7 for group comparison studies[11]. P values < 0.05 were considered to be significant. The different components of the CCC (Pearson correlation coefficient, location shift and scale shift) were calculated. A value of 0 represents no location shift. A value of 1 represents no scale shift. The first measurement was plotted against the second measurement and we used major axis analyses to calculate the best fitting line[12]. Visual assessment was obtained by use of Bland-Altman plots. Mean differences were calculated and should be close to zero. Limits of agreement were calculated as mean difference +/- 1.96*SD of the mean difference. Ninety-five percent of the differences (calculated as measurement 1 - measurement 2) should lie between these limits. A regression coefficient was calculated to estimate a relationship between the difference and the mean.

RESULTS

Development

The original FAIM-CF, -TF and-AF contain six questions (figure 1). The wording of the questions was changed for children to improve understanding. EO questions 2 and 3 were adapted from questions which were successfully developed for validation of the Vespid allergy Quality of Life Questionnaire (VQLQ)[5] and the Food Allergy Quality of Life-Parental Burden questionnaire (FAQL-PB)[13]. Two other EO questions (1 and 4) were developed, which were likely to be an additional source of HRQL differences in food allergic patients. Additionally, two independent measure questions (IM 1 and 2) were developed, which reflect aspects of the perceived severity of food allergy not captured by the other four questions.

Validity and relevance

EO question 3 did not correlate with any of the items of the FAQLQ-TF[3] and was therefore eliminated. Additionally, EO question 4 did not correlate with any of the items of the FAQLQs. This was considered to be due to the original positive formulation of this question versus the negative formulation of the other EO questions. The positive formulation (...can effectively deal...) and a negative formulation (...cannot effectively deal...) were compared in an additional analysis of 28 children, 34 adolescents and 32 adults and showed significantly better correlations of the negative formulation with the total FAQLQ-CF, -TF and -AF scores than the positive formulation (data not shown). Therefore, we finally included EO question 4 in its negative formulation. The other questions were shown to be relevant. The final mean FAIM scores correlated significantly with the individual items of the FAQLQs[2-4].

Reliability

Patients

We contacted 148 patients, of which 131 patients completed and returned the first questionnaires and 114 responded to the second questionnaires. Thirteen patients were excluded because they did not respond in time or had a grade III or IV allergic reaction between the first and second measurement or within two months before the first measurement. This resulted in 101 patients (31 children, 34 adolescents and 36 adults) that were eligible for analysing test-retest reliability. Table 1 shows types and numbers of food allergies.

Table 1. Type and number of food allergies

	Children (n= 31)	**Adolescents** (n= 34)	**Adults** (n= 36)
Type food allergy, n (%)			
Peanut	25 (81)	30 (88)	25 (69)
Nut	17 (55)	28 (82)	25 (69)
Milk	15 (48)	15 (44)	15 (42)
Egg	14 (45)	16 (47)	7 (19)
Wheat	5 (16)	4 (12)	7 (19)
Soy	9 (29)	13 (38)	8 (22)
Sesame	7 (23)	9 (26)	6 (17)
Fish	2 (6)	5 (15)	9 (25)
Shell fish	6 (19)	8 (24)	12 (33)
Celery	0 (0)	4 (12)	8 (22)
Fruit	14 (45)	13 (38)	26 (72)
Vegetables	6 (19)	6 (18)	10 (28)
Others	25 (81)	24 (71)	13 (36)
Number of food allergies, n(%)			
1 food	6 (19)	3 (9)	1 (3)
2 foods	4 (13)	4 (12)	3 (8)
3 foods	4 (13)	8 (24)	10 (28)
> 3 foods	17 (55)	19 (56)	22 (61)

Analysis

Table 2 shows the results of the test-retest analysis. ICCs were 0.87, 0.86 and 0.76 for FAIM-CF, -TF and -AF, respectively. CCCs were nearly identical. Location shift and scale shift could all be considered minimal according to Lin's examples[10]. Pearson correlation could be considered moderate for FAIM-CF and -TF and acceptable for FAIM-AF according to Lin's examples [10]. Figure 2 illustrates the correlation between the first and second measurement. Major Axis analysis revealed no significant difference of the slope and the intercept of the best fitting line from the concordance line for the FAIMs. The slope and intercept of the best fitting lines of all FAIMs did not differ significantly from each other. Bland-Altman plots are shown in Figure 3. Mean differences of both scores were all close to zero. About 95 % of the differences lie within the 1.96 SD limits of agreement. Limits of agreement of the FAIM-AF were wide. There is no significant correlation between the mean of both scores and the difference of both scores.

Table 2. Test-retest reliability results of the Food Allergy Independent Measure-Child Form, -Teenager Form and -Adult Form (FAIM-CF, -TF and -AF).

	FAIM-CF	FAIM-TF	FAIM-AF
M1 (SD1)	3.72 (0.93)	4.15 (0.93)	3.97 (1.05)
M2 (SD2)	3.80 (1.10)	4.10 (1.09)	4.04 (1.20)
Mean of both scores (SD) (M1 +M2/2)	3.76 (0.99)	4.13 (0.97)	4.00 (1.05)
Mean difference (SD) (M1-M2)	-0.08 (0.52)	0.05 (0.55)	-0.07 (0.79)
Limits of agreement (MD +/- 1.96 SD)	-1.09 to 0.93	-1.02 to 1.12	-1.61 to 1.47
ICC (95 % CI)	0.87 (0.76-0.94) p < 0.001	0.86 (0.74-0.93) p < 0.001	0.76 (0.58-0.87) p < 0.001
Error variance	0.13	0.15	0.31
CCC (95% CI)	0.87 (0.79-0.95) p < 0.001	0.85 (0.76-0.94) p < 0.001	0.75 (0.61-0.90) p < 0.001
Scale shift	1.18	1.17	1.14
Location shift	-0.08	0.05	-0.06
Pearson	0.88	0.87	0.76

M1: Total FAIM score measurement 1
M2: Total FAIM score measurement 2
MD: Mean Difference
ICC: Intraclass Correlation Coefficient
CCC: Concordance Correlation Coefficient
SD: Standard Deviation
Scale shift (SD2/SD1)
Location shift: $\frac{(M1-M2)}{\sqrt{SD1 \times SD2}}$

Figure 2. FAIM score of the first measurement against FAIM score of the second measurement in (A) children, (B) adolescents and (C) adults

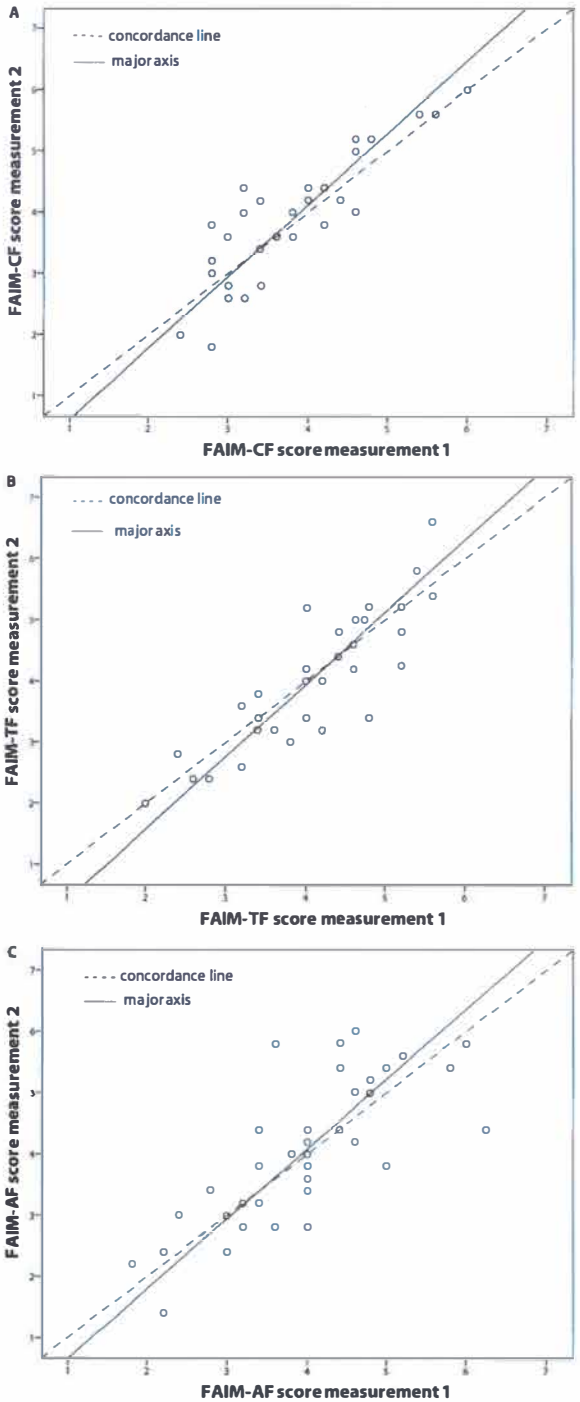
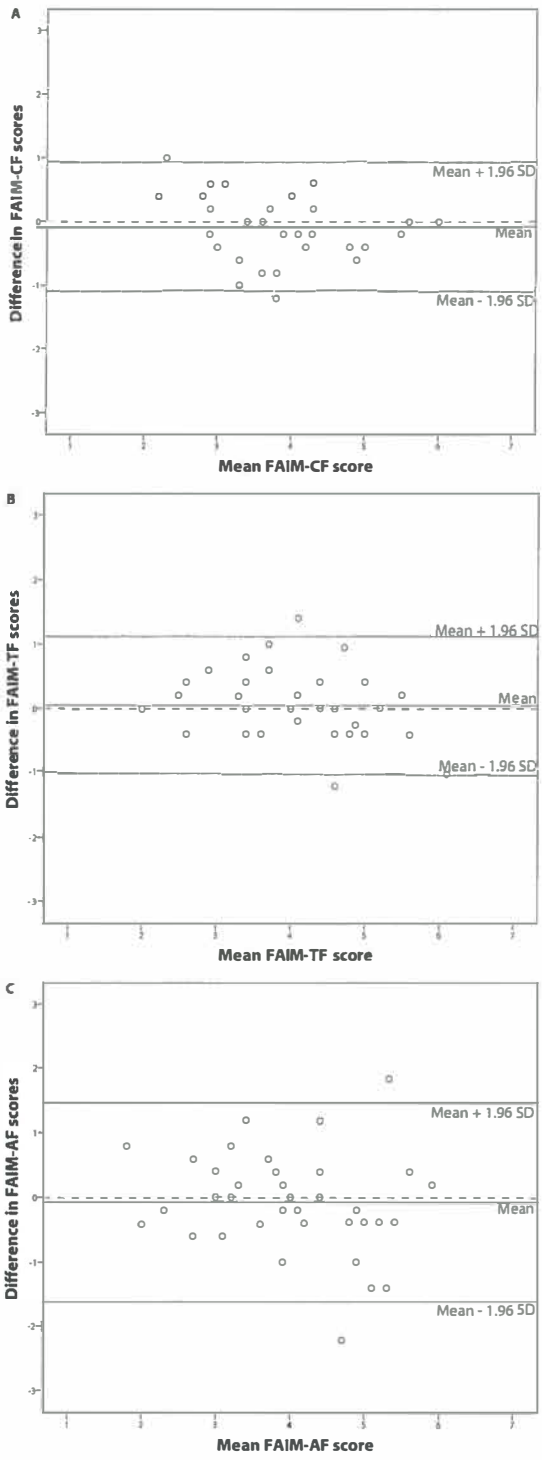


Figure 3. Bland-Altman plots for the FAIMs in (A) children, (B) adolescents and (C) adults



DISCUSSION

This article describes the development, face validity and test-retest reliability of the FAIMs. Questions were chosen for good face validity and selected on the basis of relevance. The FAIMs showed good reliability with ICCs and CCCs above 0.70 and with mean differences all close to zero. There was little evidence for scale shift and location shift supporting the accuracy of the FAIMs.

Generally, independent measures used to validate HRQL questionnaires are some sort of objective measurement of the severity of a disease. An objective measurement is often related to the burden of symptoms characterising the disease. However, in food allergy no such clinical measure based on symptoms exists. Moreover, such a clinical measure would even be inappropriate because food allergic patients only experience symptoms on accidental exposure, while their HRQL is continuously affected by their condition. An independent measure based on food allergic outcomes attempts to capture the aspects of disease severity which drive HRQL in an ongoing way. HRQL instruments built upon the method of EO questions have proved to be useful and consistent in measuring HRQL[5,13].

It was an unexpected finding that in adolescents EO question 3 was not correlated with any of the items of the FAQLQ-TF. As this question has successfully been used before in other age groups, we expected the question to be valid and relevant. However, this finding might indicate that adolescents are not afraid of dying of anaphylaxis and underestimate exposure in contrast to adults and children. Previously, it has been reported that adolescents perceived their anaphylaxis as 'no big deal'[14] despite the fact that they are at highest risk of dying from food allergy[15].

Another remarkable finding was shown in the results of the validity of EO question 4. These results illustrate that the wording of a question is very important. Changes in wording may result in misreading of the question or misdirection of the answer in sometimes unexpected ways.

According to the reliability results, the FAIM-AF showed the lowest ICC and CCC and the widest limits of agreement. This may have been caused by two outliers in the FAIM-AF. This assumption was supported by a re-analysis excluding the two outliers, which showed an ICC of 0.84 ($p<0.001$), a nearly identical CCC and limits of agreement of -1.31 to 1.19. Another explanation might be that children and adolescents are more used to filling out questionnaires as they are frequently examined at school, causing higher reliability statistics.

A limitation of the method of EO questions might be that EO questions are subjective and therefore prone to inaccuracy. However, expectations are likely to be the driving force in HRQL (i.e. patients who expect to die after exposure, would be expected to have a poor HRQL, independent of the truth of this expectation)[16]. Moreover, there is no appropriate objective measure in food allergy. Therefore, the FAIMs are the best independent measures for food allergy thus far.

In summary, we described the development of a food allergy specific independent measure for children, adolescents and adults. Overall, the FAIMs showed good face validity, relevance and reliability. Therefore, these results support the suitability of the FAIMs for evaluating construct validity of HRQL questionnaires for food allergy.

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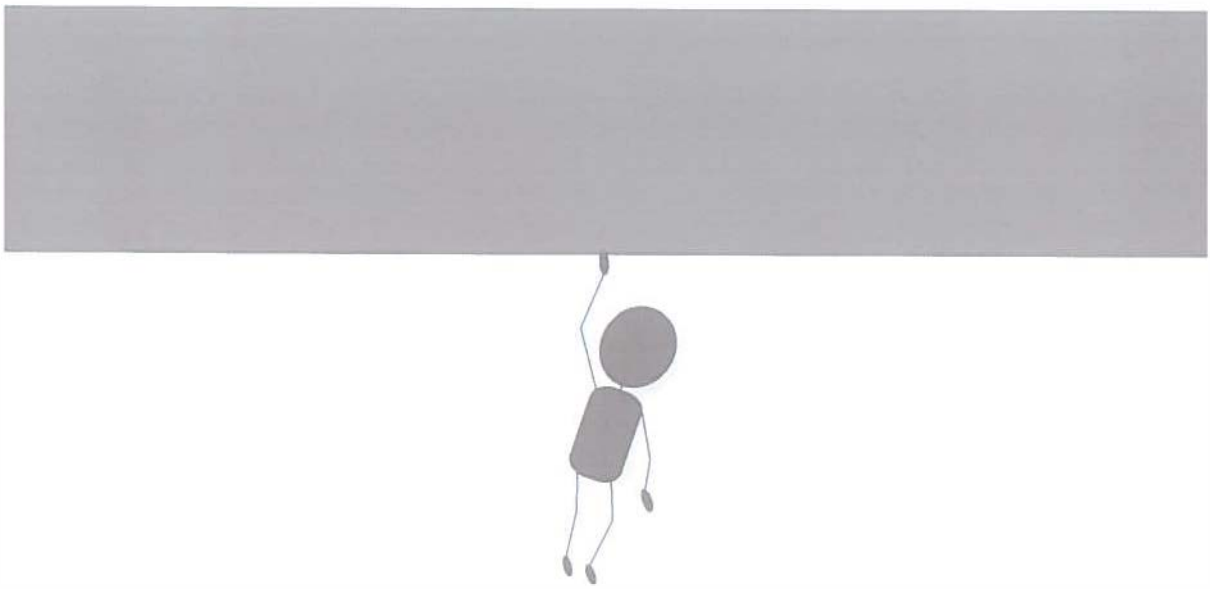
REFERENCE LIST

1. Bowling A. Theory of measurement. In: Bowling A, editors. Measuring health: A review of quality of life measurement scales. Buckingham: Open University Press, 1997:9-14.
2. Flokstra-de Blok BMJ, DunnGalvin A, Vlieg-Boersta BJ et al. Development and validation of a self-administered Food Allergy Quality of Life Questionnaire for children. Clin Exp Allergy 2009; 39:127-37.
3. Flokstra-de Blok BMJ, DunnGalvin A, Vlieg-Boerstra BJ et al. Development and validation of a self-administered Food Allergy Quality of Life Questionnaire for adolescents. J Allergy Clin Immunol 2008; 122:139-44.
4. Flokstra-de Blok BMJ, DunnGalvin A, Vlieg-Boerstra BJ et al. Development and validation of the Food Allergy Quality of Life Questionnaire-Adult Form (FAQLQ-AF). Allergy 2009; 64:1209-17.
5. Oude Elberink JN, de Monchy JG, Golden DB, Brouwer JL, Guyatt GH, Dubois AE. Development and validation of a health-related quality-of-life questionnaire in patients with yellow jacket allergy. J Allergy Clin Immunol 2002; 109:162-70.
6. Oude Elberink JN. Significance and rationale of studies of health-related quality of life in anaphylactic disorders. Curr Opin Allergy Clin Immunol 2006; 6:298-302.
7. Mueller HL. Diagnosis and treatment of insect sensitivity. J Asthma Res 1966; 3:331-3.
8. Van der Velde JL, Flokstra-de Blok BMJ, Vlieg-Boerstra BJ et al. Test-retest reliability of the Food Allergy Quality of Life Questionnaires (FAQLQ) for children, adolescents and adults. Qual Life Res 2009; 18:2:245-51.
9. Schuck P. Assessing reproducibility for interval data in health-related quality of life questionnaires: which coefficient should be used? Qual Life Res 2004; 13:571-86.
10. Lin LI. A concordance correlation coefficient to evaluate reproducibility. Biometrics 1989; 45:255-68.
11. Scientific Advisory Committee of the Medical Outcome Trust. Assessing health status and quality-of-life instruments: attributes and review criteria. Qual Life Res 2002; 11:193-205.
12. Warton DI, Wright IJ, Falster DS, Westoby M. Bivariate line-fitting methods for allometry. Biol Rev Camb Philos Soc 2006; 81:259-91.
13. Cohen BL, Noone S, Munoz-Furlong A, Sicherer SH. Development of a questionnaire to measure quality of life in families with a child with food allergy. J Allergy Clin Immunol 2004; 114:1159-63.
14. Akeson N, Worth A, Sheikh A. The psychosocial impact of anaphylaxis on young people and their parents. Clin Exp Allergy 2007; 37:1213-20.
15. Bock SA, Munoz-Furlong A, Sampson HA. Further fatalities caused by anaphylactic reactions to food, 2001-2006. J Allergy Clin Immunol 2007; 119:1016-8
16. Carr AJ, Gibson B, Robinson PG. Measuring quality of life: is quality of life determined by expectations or experience? BMJ 2001; 322:1240-3.



Chapter 5

Parents report better health-related quality of life for their food allergic children than children themselves

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ABSTRACT

Objective: Food allergy affects 5-6% of children and impairs Health-Related Quality-of-Life (HRQL). Children and parents may differ in their views concerning the child's HRQL. In food allergy, child- and parent-proxy-reported HRQL have never been compared using valid disease-specific instruments. The aim of this study was to compare child- and parent-proxy-reports on HRQL in food allergic children (8-12 years).

Methods: The Food Allergy Quality of Life Questionnaire-Child Form (FAQLQ-CF), and -Parent Form (FAQLQ-PF) and the Food Allergy Independent Measure-Child Form and -Parent Form (FAIM-CF and -PF) were completed by Dutch food allergic child-parent pairs. Child- and parent-proxy-reports were correlated and tested for significant differences. Construct validity (correlation FAQLQs and FAIMs) and internal consistency (Cronbach's α) were assessed and compared.

Results: Seventy-four child-parent pairs were included. FAQLQ-CF score was significantly higher than FAQLQ-PF score (3.74 versus 2.68, $p<0.001$, where 1 signifies no impairment and 7 signifies extreme impairment). FAIM-CF and -PF scores were nearly identical (3.29 versus 3.33, $p=0.594$). There was moderate agreement between FAQLQ-CF and -PF scores (ICC=0.57 [$p<0.001$]) and good agreement between FAIM-CF and -PF scores (ICC=0.80 [$p<0.001$]). Construct validity was confirmed for the FAQLQ-CF (rho=0.60, $p<0.001$) and -PF (rho=0.58, $p<0.001$). Internal consistency was excellent for the FAQLQ-CF ($\alpha=0.95$) and -PF ($\alpha=0.95$).

Conclusions: Parents reported significantly less impact of food allergy on the child's HRQL than children themselves, whereas reported perceptions of disease severity were nearly identical. This may reflect real differences in perspectives between children and parents and may indicate that parents tend to underestimate their child's HRQL impairment. It is important for clinicians to include both the child's and their parent's perceptions in order to make a complete assessment of the impact of food allergy on the child's HRQL and to identify areas of disagreement which need special attention in clinical practice.

INTRODUCTION

Food allergy affects up to 5-6 % of children in western countries[1,2] and may cause severe anaphylactic reactions. Living with the fear of allergic reactions and living with the need to avoid the culprit foods in numerous situations may interfere with daily life of food allergic children and their families[3,4]. Therefore, Health-Related Quality of Life (HRQL) measurements are important to investigate the impact of daily problems of food allergic children and their families[5-7]. As no clinical objective measure is available which reflect the ongoing disease severity of food allergy, measuring HRQL is also important to determine the effects of diagnostic or therapeutic interventions on HRQL.

HRQL of children can be measured with questionnaires which are self-reported or proxy-reported. Assessment of HRQL in children has traditionally relied on parent-reporting, as it was thought that children lack the necessary language skills and cognitive abilities for accurate self-reporting[8,9]. However, it has been reported that children ≥8 years are able to assess their HRQL appropriately[10,11]. Consequently, a number of HRQL questionnaires have been developed for and validated in children[12,13]. As parents seem to be less able to make judgments regarding the experience of symptoms, relationships with peers or worries about the future of their child[14,15], self-report is the primary method of assessing the subjective aspects of health. On the other hand, it is obvious that parent-reports are indispensable in children who are unable to assess their own HRQL[16]. Moreover, parental attitudes may influence their child's own attitudes and the utilization of health-care services for their child. Additionally, parents may provide information not provided by children themselves. It is thus important to study child- and parent-proxy-reports on the child's HRQL and to assess the quality of parent-proxy-reporting. However, in food allergic children, a comparison of child- and parent-reported HRQL has never been made using validated disease-specific instruments.

Two disease-specific HRQL instruments, the Food Allergy Quality of Life Questionnaire-Child Form (FAQLQ-CF) and -Parent Form (FAQLQ-PF) have recently been developed and validated as part of the EuroPrevall project[7,13,17,18]. The FAQLQ-CF was originally developed in the Netherlands for children aged 8-12 years and provides a valid and reliable self-report on the child's HRQL. The FAQLQ-PF was originally developed in Ireland for parents of children aged 0-12 years and provides a valid and reliable parent-proxy-report on the child's HRQL. Therefore, the aim of this study was to compare outcome (i.e. total FAQLQ scores and domain scores) and psychometric properties of the FAQLQ-CF and -PF and to investigate areas of (dis)agreement between child- and parent-reports.

METHODS

Patients and procedures

Dutch food allergic children (8-12 years) and their parents were recruited from our paediatric allergy clinic between May 2007 and March 2009. All children with at least one physician diagnosed food allergy were included. All common food allergies and different types and severities of symptoms were represented.

The Dutch versions of the FAQLQs and the Food Allergy Independent Measure questionnaires (FAIMs) were sent by mail to be completed at home[13,19]. Participation was completely voluntary. Child-parent pairs were requested not to discuss questions and responses with each other. Child-parent pairs were excluded when less than 85% of the questions were completed.

This study was approved by the local medical ethics review commission (METc 2005/051) who deemed that permission from the commission was not required.

Questionnaires

The FAQLQ-CF provides a self-report on the child's HRQL and contains 24 items and 4 domains (Risk of Accidental Exposure, Emotional Impact, Allergen Avoidance and Dietary Restrictions)[13]. Items were scored on a seven-point scale ranging from not troubled to extremely troubled. In order to improve understanding, the scale was illustrated by drawings of faces ('smileys'), ranging from a smiling face to a sad face. The total FAQLQ score is the sum of all the items divided by the number of items and ranges from 1 (minimal impairment in HRQL) to 7 (maximal impairment in HRQL).

The FAQLQ-PF provides a parent-report on the child's HRQL and contains 14 items, 26 items and 30 items for children aged 0-3 years, 4-6 years and 7-12 years, respectively[7]. Items are divided into 3 domains (Emotional Impact, Food Anxiety and Social & Dietary Limitations) and scored in the same way as the FAQLQ-CF. The FAQLQ-PF was translated from English into Dutch by a native Dutch speaker and back translated by a native English speaker, using established guidelines[20]. The original English version was compared with the back-translated English version by an expert panel. No important linguistic or semantic differences emerged.

The Food Allergy Independent Measure-Child Form and Parent-form (FAIM-CF and -PF) were originally developed as an independent measure for food allergy in order to evaluate the construct validity of the FAQLQs[19]. The FAIMs contain four expectation of outcome questions, concerning the child's perceived expectation of the chance of accidental exposure and of what will happen following accidental exposure and two questions reflecting perceived disease severity. Such expectations are likely to be the source of quality of life differences in anaphylactic disorders and are therefore an appropriate independent measure for anaphylactic disorders[21]. Furthermore, HRQL instruments built

upon the method of expectation of outcome questions have proved to be useful and consistent in measuring HRQL[6,7,13,22-24]. Questions were scored on a seven-point scale. The translation procedure, as described for the FAQLQ-PF, was followed for the FAIM-PF as well.

Additionally, child- and parent characteristics were asked on age, sex, type and number of food allergies etc. Parental health and well-being was measured using a question which was previously used during the development of the FAQLQ-PF[7]: "How would you describe your general health and well-being?" (seven-point scale ranging from excellent to very poor).

Statistical analysis

Comparison of child-self and parent-proxy-reports

Data were analyzed using SPSS software for Windows (Version 16.0). Total FAQLQ-CF and -PF scores (and domain scores) were tested for significant differences using Wilcoxon signed-rank tests. Total FAQLQ-CF and -PF scores were correlated using Spearman's correlation coefficient and the Intraclass correlation coefficient (ICC, two-way mixed effects model). Correlations were classified as follows: <0.4=poor to fair, 0.4-0.6=moderate, 0.6-0.8=good and >0.8=excellent. Bland-Altman plots illustrated the differences of each child-parent pair (FAQLQ-CF score minus FAQLQ-PF score), which were plotted against the mean FAQLQ score of each child-parent pair. Limits of agreement were calculated as mean difference +/- 1.96*standard deviation of the mean difference.

The procedure, as described above, was followed for the comparison of the FAIMs as well.

Influence of child characteristics on child-parent agreement

Univariate linear regression analyses were performed to investigate which child characteristics influenced child-parent agreement. The mean difference between child- and parent-reported HRQL was used as the dependent variable and child characteristics (age, sex, anaphylaxis, last experience of anaphylaxis, number of food products which must be avoided) were used as independent variables. The same procedure was followed for the FAIMs.

Psychometric properties of the questionnaires

Construct validity of the FAQLQs was investigated using Spearman's correlation coefficient between the total FAQLQ-CF score and the total FAIM-CF score and between the total FAQLQ-PF score and the total FAIM-PF score, respectively. A moderate correlation (0.4-0.6) was to be expected[25]. Internal consistency was investigated using Cronbach's alpha ($\alpha \geq 0.70$ was considered to be good)[26]. Discriminative abilities were investigated by comparing total questionnaire scores for boys versus girls, for patients who have one

versus more than one food allergy, for patients who must avoid ≤10 versus >10 food products and for patients who experienced anaphylaxis versus patients who did not. Experience of anaphylaxis was determined using the definition of the 'Symposium on the Definition and Management of Anaphylaxis'[27]. Floor and ceiling effects were calculated as percentage of patients with questionnaire scores of 1 (minimal impact on HRQL) and 7 (maximal impact on HRQL), respectively.

RESULTS

Patients

The questionnaire package was sent to 109 Dutch child-parent pairs and returned by 84 child-parent pairs (response rate 77%). Ten child-parent pairs were excluded because less than 85% of one of the questionnaires was completed. Thus, 74 child-parent pairs were eligible for analysis. Descriptive characteristics of the child-parent pairs are shown in Table 1.

Table 1. Child- and parent-characteristics

Participants, n (%)	74	(100)
Mean age, years (SD)	10.4	(1.6)
Child sex, male/female (%)	46/28	(62/38)
Type of food allergies, n (%)		
Peanut	54	(73)
Nut	54	(73)
Milk	9	(12)
Egg	12	(16)
Wheat	4	(5)
Soy	11	(15)
Sesame	3	(4)
Fish	1	(1)
Shell fish	4	(5)
Fruit	10	(14)
Vegetables	4	(5)
Number of food allergies, n (%)		
1 food	23	(31)
2 foods	28	(38)
3 foods	9	(12)
> 3 foods	14	(19)
Number of food products which must be avoided, n (%)		
0-2	30	(41)
3-6	16	(22)
7-10	6	(8)
>10	19	(26)

Table 1. Child- and parent-characteristics *(Continued)*

Type of symptoms, n (%)		
Cardiovascular	21	(28)
Respiratory	60	(81)
Gastro-intestinal	45	(61)
Skin	49	(66)
Other[1]	65	(88)
Anaphylaxis, yes/no (%)	62/12	(84/16)
Last experience of anaphylaxis, years (SD)	4.8	(3.6)
Epinephrine autoinjector, yes/no (%)	56/18	(76/24)
Parent sex, male/female (%)	7/67	(9/91)
Reported parental health & wellbeing, n (%)		
Excellent	11	(15)
Very good	22	(31)
Good	37	(50)
Moderate	1	(5)
< moderate	1	(5)

1 Oral Allergy Syndrome, swollen tongue or lips and symptoms of the nose or eyes.

Comparison of the FAQLQ-CF and -PF

The total FAQLQ-CF score was significantly higher (indicating more severe impact on HRQL) than the total FAQLQ-PF score (3.74 versus 2.68, p<0.001) (Table 2). All domain scores of the FAQLQ-CF were significantly higher than the domain scores of the FAQLQ-PF. Spearman's correlation coefficient between the total FAQLQ-CF and -PF score was 0.56 (p<0.001). The ICC of 0.57 (95% CI; 0.40-0.71, p<0.001) was comparable. Figure 1A illustrates this moderate correlation. The Bland-Altman plot illustrates the mean difference (1.06, SD=1.10) between the FAQLQ-CF and -PF score (Figure 2A).

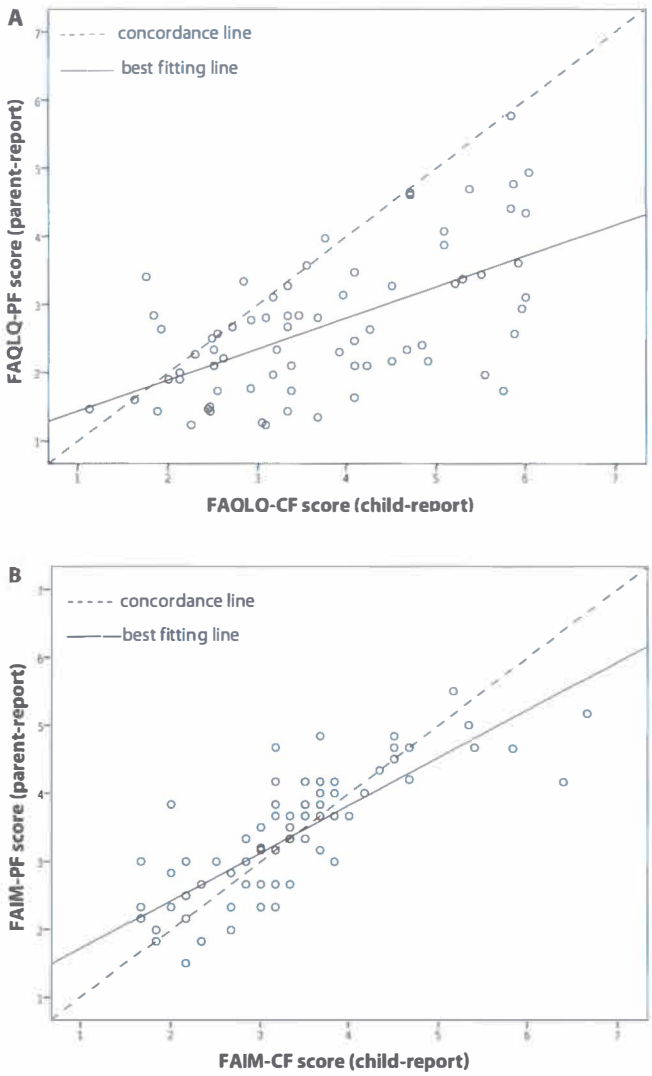
Table 2. Outcome of the questionnaires

	Mean total scores (SD)
FAQLQ-CF	3.74 (1.34)
Allergen avoidance	3.35 (1.41)
Risk accidental exposure	3.78 (1.57)
Emotional impact	4.13 (1.57)
Dietary restrictions	3.74 (1.44)
FAQLQ-PF	2.68 (1.02)
Emotional impact	2.61 (0.95)
Food anxiety	2.96 (1.15)
Social & dietary limitations	2.53 (1.29)
FAIM-CF	3.29 (1.09)
FAIM-PF	3.33 (0.94)

Comparison of the FAIM-CF and -PF

There was no significant difference between the total FAIM-CF and -PF scores (3.29 versus 3.33, p=0.594) (Table 2). Spearman's correlation coefficient between the total FAIM-CF and -PF score was 0.82 (p<0.001). The ICC of 0.80 was comparable (95% CI; 0.69-0.87, p<0.001). Figure 1B illustrates this good correlation. The Bland-Altman plot illustrates that the mean difference between the FAIM-CF and -PF was close to zero (-0.04, SD=0.65) (Figure 2B).

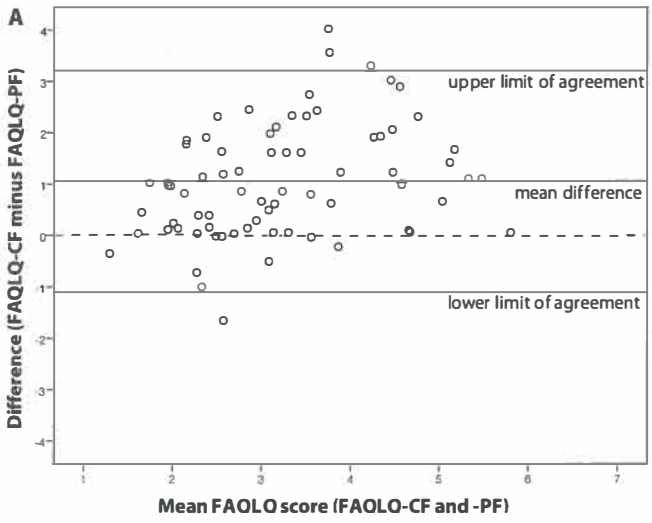
Figure 1. FAQLQ-CF versus -PF scores (A) and FAIM-CF versus -PF scores (B)



Influence of child characteristics on child-parent agreement

Univariate linear regression analyses are shown in table 3. The mean difference between child- and parent-reported HRQL was significantly associated with child age; i.e. the difference was smaller for the oldest children (11-12 years) than for the youngest children (8-10 years). The mean difference between child- and parent-reported FAIM scores was not significantly associated with any of the child characteristics.

Figure 2. Bland Altman plot for FAQLQ-CF versus -PF (A) FAIM-CF versus -PF (B)



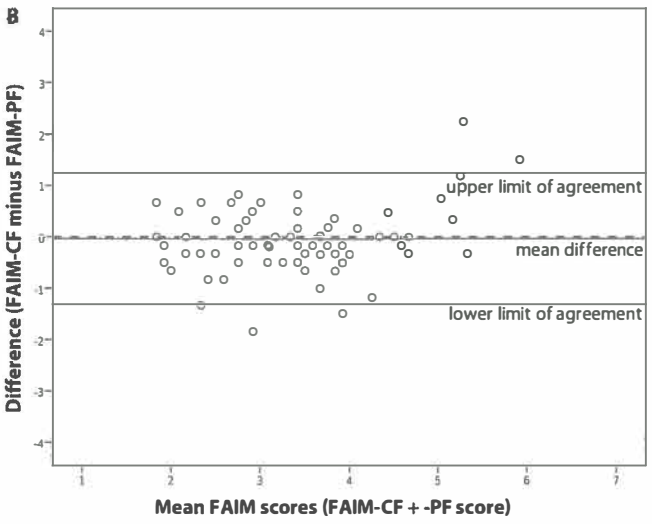


Table 3. Univariately associated factors influencing the difference between child-self and parent-proxy reported HRQL and disease severity

	HRQL (FAQLQs)			Disease severity (FAIMs)		
	B	R^2 (%)	P	B	R^2 (%)	P
Sex (girls versus boys)	0.127	7.5	0.630	0.013	2.2	0.933
Age (8-10 vs 11-12 years)	-0.547	6.2	**0.034**	-0.270	4.2	0.080
Number food products (0-10 vs >10)	0.124	0.3	0.677	0.101	0.4	0.463
Anaphylaxis (no vs yes)	0.216	0.7	0.464	0.084	0.3	0.636
Last experience of anaphylaxis (how long ago in years)	-0.043	2.0	0.249	-0.008	0.2	0.702

Table 4. Psychometric properties of the questionnaires

					Discriminative abilities			
			Floor& ceiling effects[3]		Sex	Food products[4]	Number of food allergies	Experience of Anaphylaxis
	Rho[1]	α[2]	%	/%	boys vs girls	0-10 vs >10	1 vs >1	No vs Yes
FAQLQ-CF	0.60	0.95	0	/0	3.76 vs 3.70 (p=0.780)	3.45 vs 4.63 **(p=0.007)**	3.49 vs 3.87 (p=0.210)	3.13 vs 3.85 (p=0.078)
Allergen avoidance	0.52	0.88	2.70	/0	n.p.[5]	n.p.	n.p.	n.p.
Risk accidental Exposure	0.62	0.83	1.35	/0	n.p.	n.p.	n.p.	n.p.
Emotional impact	0.60	0.87	1.35	/1.35	n.p.	n.p.	n.p.	n.p.
Dietary restrictions	0.49	0.82	1.35	/1.35	n.p.	n.p.	n.p.	n.p.
FAQLQ-PF	0.58	0.95	0	/0	2.65 vs 2.73 (p = 0.902)	2.45 vs 3.21 **(p=0.023)**	2.33 vs 2.86 **(p=0.037)**	2.23 vs 2.77 (p=0.102)
Emotional impact	0.47	0.87	0	/0	n.p.	n.p.	n.p.	n.p.
Food anxiety	0.68	0.86	1.35	/0	n.p.	n.p.	n.p.	n.p.
Social & dietary limitations	0.48	0.92	5.41	/0	n.p.	n.p.	n.p.	n.p.
FAIM-CF	-	0.81	0	/0	3.18 vs 3.53 (p=0.264)	2.89 vs 3.98 **(p=0.001)**	3.05 vs 3.42 (p=0.122)	2.74 vs 3.42 **(p=0.022)**
FAIM-PF	-	0.79	0	/0	3.22 vs 3.53 (p=0.184)	2.98 vs 3.90 **(p=0.006)**	3.08 vs 3.44 (p=0.131)	2.96 vs 3.41 **(p=0.017)**

1 Construct validity of the FAQLQs; i.e. Spearman correlations between the FAQLQ score and the FAIM score, p<0.001 for all values.
2 Internal consistency, cronbach's α.
3 Percentage of patients with the minimal (floor) or maximal (ceiling) FAQLQ-PF score
4 Number of food products that must be avoided
5 N.p. not performed
Bold scores represent significant P values (p<0.05).

Psychometric properties of the questionnaires

Construct validity was confirmed for the FAQLQs (Table 4). Internal consistency was considered to be excellent for the FAQLQs and good for the FAIMs. There were no remarkable floor- or ceiling effects for the FAQLQs and the FAIMs.

None of the questionnaires discriminated between boys and girls. The FAQLQ-PF discriminated between patients who had one versus more than one food allergy; i.e. scores were significantly higher (indicating more severe impact on HRQL) in patients who had more than one food allergy. A trend in the same direction was shown for the FAQLQ-CF, FAIM-CF and -PF. All questionnaires discriminated between patients who must avoid ≤10 versus >10 food products. The FAIM-CF and -PF discriminated between patients who had experienced anaphylaxis versus patients who did not. A trend in the same direction was shown for the FAQLQ-CF and -PF.

DISCUSSION

This is the first study comparing child-reports and parent-proxy-reports on the child's HRQL in food-allergic children (8-12 years) using equally valid disease-specific instruments. A moderate correlation was shown between the total FAQLQ-CF and -PF score, which means that children and parents had concordant judgments concerning the child's HRQL. However, children systematically reported a significantly greater impact of food allergy on their HRQL than their parents, while reported perception of disease severity and expectation of outcome of an allergic reaction were nearly identical in children and their parents. The difference between child- and parent-proxy-reported HRQL (1.06) is highly likely to be a clinically important difference as it exceeds the minimal important difference (MID) that patients find meaningful using HRQL questionnaires with a seven-point scale (0.5)[28] and exceeds at least twice the established MID for the FAQLQ-PF (0.45)[17].

Generally, child- and parent-proxy reports on the child's HRQL are moderately correlated[29]. Disagreement between child- and parent-proxy reports may reflect real differences in perspectives of children and parents, but some other causes of disagreement should be considered[9], including child characteristics, parent characteristics, questionnaire characteristics and response styles of children and parents.

Firstly, child characteristics may influence disagreement between child- and parent-reports on the child's HRQL. In our study, the age of the child may have influenced this disagreement. We found that the difference between child- and parent-proxy-reported HRQL was smaller for the oldest children (11-12 years) than for the youngest children (8-10 years). This is in line with previous results, which showed that in asthmatic children under the age of 11, complementary information can be obtained by questioning both children and parents, but for children aged over 11, parents provide little information beyond that obtained from questioning the child[30]. A possible explanation may be that as

children mature they become more articulate in expressing their feelings or concerns and consequently, parents may have a better insight into their child's HRQL[30]. Additionally, it has previously been shown that children's conceptions on health and disease are shown to be related to age and this may suggest a developmental trend in their understanding of the concepts of health maintenance and illness; i.e. the older the child the more the child's thinking about disease approaches the adult way of thinking. Furthermore, the impact of illness experience seemed to vary with age as well[31-33]. However, the fact that there was little difference between the FAIM reporting in children and parents, suggests that there is no significant lack of understanding of the disease severity in these children. Moreover, it has previously been shown that children ≥8 years are able to assess their HRQL appropriately[10,11]. Additionally, a consultant for sick children and a linguist previously reviewed the FAQLQ-CF and FAIM-CF in order to improve clarity and ease of use[13]. The difference between child- and parent-proxy-reported HRQL may thus suggest a real difference in perspectives and may well be age-related.

Secondly, parent-characteristics may influence disagreement between child- and parent-reports. In our study, almost all parents were mothers and they reported less impact on the child's HRQL than their children. It has previously been shown that mothers tend to report a greater impact on the child's HRQL than fathers[34-36] and it is thus unlikely that maternal (as opposed to paternal) reporting was the cause of the greater impact of food allergy on the child's HRQL reported by children than by parents. Impaired parental health and well being may also influence agreement between child- and parent reports as this may be a psychosocial stressor for children and parents[36-38]. In our study, all parents classified their own health as moderate to excellent. Therefore, parent-characteristics did not seem to be an important cause of the difference between child- and parent-proxy-reported HRQL.

Thirdly, questionnaire characteristics such as validity, sensitivity and content may influence agreement between child- and parent-proxy-reports on the child's HRQL. The FAQLQ-CF and -PF were both developed using the same methods and were previously shown to be valid and reliable[7,13]. However, the FAQLQ-CF and -PF are developed in a different language and culture. It has previously been shown that translation of an instrument may compromise the validity and sensitivity (the ability to detect differences between groups in a cross-sectional study design) of a translated instrument due to semantic differences or flaws in the cross cultural adaptation process[39,40]. Additionally, this may be due to the fact that some HRQL items may be regarded as unimportant by patients or proxies from a particular cultural setting (and therefore not included in the original instrument), whereas the same items would have been regarded as important by patients or proxies from another cultural setting. Therefore, detailed guidelines have been proposed[20] in order to achieve a high quality of the translated instruments. The translated Dutch FAQLQ-PF was a valid, reliable and discriminative instrument for measuring HRQL in food allergic children (8-12 years) and the psychometric properties were comparable to

the original Irish FAQLQ-PF[7]. Despite the use of established guidelines[20], loss of sensitivity of a translated instrument is not completely avoidable and may cause an underestimation of the real impact of a disease on HRQL compared to the impact as measured by the translated instrument. However, indicators of sensitivity (slight floor effects, no ceiling effects and good discriminative abilities) do not suggest a relevant loss of sensitivity of the Dutch FAQLQ-PF. Moreover, the FAIM-PF has been translated and adapted in the same way as the FAQLQ-PF, but no significant difference was shown between child- and parent-proxy-reported FAIM scores. Therefore, we think that loss of sensitivity of the translated FAQLQ-PF is not likely to contribute significantly to the differences between HRQL scores reported by children and their parents. We recommend comparing the FAQLQ-CF and -PF in the English language to fully exclude loss of sensitivity in the translated instruments.

Fourthly, differences in response styles between children and parents may cause disagreement[41]; In general, young children tend to choose extreme scores (never and always instead of sometimes and often) than adults do. In our study, the risk of choosing extreme scores was minimized using visual aids ('smileys') for children. Moreover, an additional analysis showed that only 16.6% of all individual items of the FAQLQ-CF were given the lowest score and 13.0% the highest score. Therefore, it seems unlikely that differences in response styles influenced disagreement between child- and parent-proxy-reported HRQL. Future studies based on the item response theory may be useful for more in depth investigation of child- and parent-responses to the items of the FAQLQ-CF and -PF and to determine how scores on one questionnaire calibrate against scores on the other.

In addition to the factors which may have influenced agreement between child- and parent-reports, real differences in perspectives between children and their parents may at least be partially responsible for the differences in HRQL scores we found. Children and parents often agree on objective domains (symptoms or functioning), while there is less agreement for socio-emotional domains, because parents may have a lack of insight into their child's experiences and beliefs[15]. As the FAQLQ-CF and -PF mainly consist of socio-emotional domains, this may explain part of the difference between child- and parent-reports and may reflect a real difference in perspectives. A difference in perspectives is also suggested by the direction of the difference between FAQLQ and FAIM scores. In parents, the FAQLQ-PF score (2.68) was lower than the FAIM-PF score (3.33), possibly suggesting that parents may underestimate the impact of food allergy on their child's HRQL. In children, the opposite is seen with higher FAQLQ-CF (3.74) than FAIM-CF scores (3.29), possibly suggesting that children overestimate their HRQL. This seemingly real difference in perception between children and their parents may also be contributing to the difference between child- and parent-proxy-reported HRQL.

A difference in perspectives is also reflected by the differences in content of the FAQLQ-CF and -PF for children aged 8-12 years. The two FAQLQs were developed using the same preferred methods in order to measure the same concept 'the child's quality of

life'; Firstly, all potential items for the new questionnaires were assembled using literature search, expert opinion and interviews with food allergic children aged 8-12 years (FAQLQ-CF) or parents of food allergic children aged 8-12 years (FAQLQ-PF). Secondly, the clinical impact method[42,43] was used to select the most important items for children and their parents for the final versions of the FAQLQ-CF and -PF, respectively (i.e. For each item, respondents were asked to indicate whether an item was important to them ('yes or no'), followed by a 5-point response option indicating the degree of importance related to that item. Items identified most frequently and rated the most important were selected for the final FAQLQ-CF and -PF). As some HRQL items were regarded as important by parents, but regarded as unimportant by children, these items were included in the FAQLQ-PF, but not in the FAQLQ-CF and vice versa. These differences in content of the FAQLQs thus highlight the areas of disagreement in perspectives between children and parents on HRQL (such as worries about the future, self-confidence compared to other children of his/ her age, feeling left out). Therefore, the FAQLQs are not interchangeable, but complement each other in the assessment of the child's HRQL from two perspectives and highlight areas of disagreement which need special attention.

Despite an increase in the number of studies evaluating child- and parent-proxy-reports on the child's HRQL[9], only some studies used reliable and well-validated HRQL instruments. Generally, child- and parent-proxy reports on the child's HRQL are moderately correlated[29]. In food allergy, only one study evaluated child- and parent-proxy-reports on the child's HRQL[34]. King et al. showed that mothers estimated the impact of peanut allergy on their child (8-12 years) as more severe than the children themselves, their siblings and their fathers. Part of the difference between the previous and the current study results may be explained by the fact that different HRQL instruments were used in the two studies. King et al. used validated generic HRQL instruments and unvalidated disease-specific HRQL instruments, whereas our study employed validated disease-specific HRQL instruments. Additionally, the previous study was performed in another cultural setting, which may cause different results compared to our study. Examples of such cultural differences may include differences in the allergy services of the United Kingdom and the Netherlands causing different levels of medical awareness in English and Dutch parents. Also, it has been shown that the psychosocial determinants of HRQL, such as coping strategies, attitudes, knowledge, social support, socio-economic status, education and beliefs may differ between cultures[44-47]. Finally, studies on cultural differences in children's emotional reactions to difficult situations have shown that children from different cultures differ in the way they communicate negative emotions[48]. Dutch and English children may thus express their emotions differently to their parents, which might have influenced the difference between the previous and the current study results.

In summary, this study clearly demonstrated that children reported more impact of food allergy on their HRQL than their parents, while the psychometric properties of the

FAQLQ-CF and -PF were nearly identical. This difference between child- and parent-proxy-reports on the child's HRQL appears to reflect real differences in perspectives between children and parents and was related to the age of the child. Since parental and child perspectives are thus likely to be different, it is important for clinicians to include both the child's and their parent's perceptions in order to make a complete assessment of the impact of food allergy and the effects of diagnostic or therapeutic interventions on the child's HRQL. Additionally, studying both perspectives allows identification of areas that need special attention.

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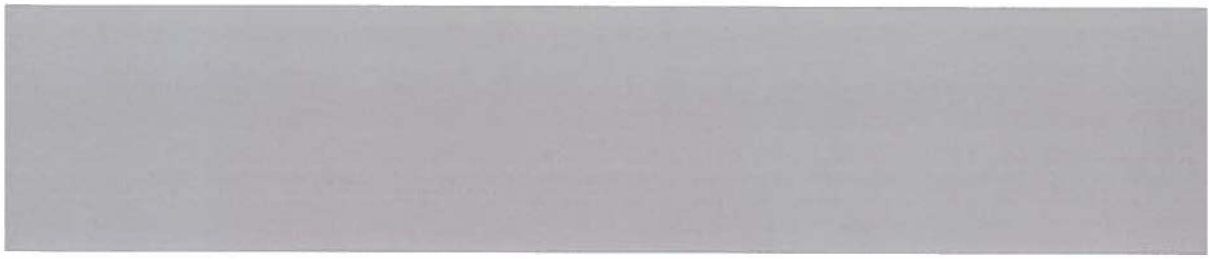
REFERENCE LIST

1. Sicherer SH, Sampson HA. Food allergy. J Allergy Clin Immunol 2010; 125:S116-25.
2. Wang J, Sampson HA. Food allergy: recent advances in pathophysiology and treatment. Allergy Asthma Immunol Res 2009; 1:19-29.
3. Ostblom E, Egmar AC, Gardulf A, Lilja G, Wickman M. The impact of food hypersensitivity reported in 9-year-old children by their parents on health-related quality of life. Allergy 2008; 63:211-8.
4. Cummings AJ, Knibb RC, King RM, Lucas JS. The psychosocial impact of food allergy and food hypersensitivity in children, adolescents and their families: a review. Allergy 2010; 65:933-45.
5. Lebovidge JS, Stone KD, Twarog FJ, Raiselis SW, Kalish LA, Bailey EP, Schneider LC. Development of a preliminary questionnaire to assess parental response to children's food allergies. Ann Allergy Asthma Immunol 2006; 96:472-7.
6. Cohen BL, Noone S, Munoz-Furlong A, Sicherer SH. Development of a questionnaire to measure quality of life in families with a child with food allergy. J Allergy Clin Immunol 2004; 114:1159-63.
7. DunnGalvin A, de BlokFlokstra BM, Burks AW, Dubois AE, Hourihane JO. Food allergy QoL questionnaire for children aged 0-12 years: content, construct, and cross-cultural validity. Clin Exp Allergy 2008; 38:977-86.
8. Theunissen NC, Vogels TG, Koopman HM, Verrips GH, Zwinderman KA, Verloove-Vanhorick SP, Wit JM. The proxy problem: child report versus parent report in health-related quality of life research. Qual Life Res 1998; 7:387-97.
9. Upton P, Lawford J, Eiser C. Parent-child agreement across child health-related quality of life instruments: a review of the literature. Qual Life Res 2008; 17:895-913.
10. Riley AW. Evidence that school-age children can self-report on their health. Ambul Pediatr 2004; 4:371-6.
11. Cremeens J, Eiser C, Blades M. Characteristics of health-related self-report measures for children aged three to eight years: a review of the literature. Qual Life Res 2006; 15:739-54.
12. Ruperto N, Ravelli A, Pistorio A et al. . Cross-cultural adaptation and psychometric evaluation of the Childhood Health Assessment Questionnaire (CHAQ) and the Child Health Questionnaire (CHQ) in 32 countries. Review of the general methodology. Clin Exp Rheumatol 2001; 19:S1-9.
13. Flokstra-de Blok BM, DunnGalvin A, Vlieg-Boerstra BJ, Oude Elberink JN, Duiverman EJ, Hourihane JO, Dubois AE. Development and validation of a self-administered Food Allergy Quality of Life Questionnaire for children. Clin Exp Allergy 2009; 39:127-37.
14. Eiser C. Children's quality of life measures. Arch Dis Child 1997; 77:350-4.
15. Davis E, Nicolas C, Waters E, Cook K, Gibbs L, Gosch A, Ravens-Sieberer U. Parent-proxy and child self-reported health-related quality of life: using qualitative methods to explain the discordance. Qual Life Res 2007; 16:863-71.
16. Connolly MA, Johnson JA. Measuring quality of life in paediatric patients. Pharmacoeconomics 1999; 16:605-25.
17. DunnGalvin A, Cullinane C, Daly DA, Flokstra-de Blok BM, Dubois AE, Hourihane JO. Longitudinal validity and responsiveness of the Food Allergy Quality of Life Questionnaire - Parent Form in children 0-12 years following positive and negative food challenges. Clin Exp Allergy 2010; 40:476-85.
18. van der Velde JL, Flokstra-de Blok BM, Vlieg-Boerstra BJ et al. . Test-retest reliability of the Food Allergy Quality of Life Questionnaires (FAQLQ) for children, adolescents and adults. Qual Life Res 2009; 18:245-51.
19. van der Velde JL, Flokstra-de Blok BM, Vlieg-Boerstra BJ et al. . Development, validity and reliability of the food allergy independent measure (FAIM). Allergy 2009.
20. World Health Organization. Process of translation and adaptation of instruments. http://www.who.int/substance_abuse/research_tools/translation/en/. 2008.
21. Oude Elberink JN. Significance and rationale of studies of health-related quality of life in anaphylactic disorders. Curr Opin Allergy Clin Immunol 2006; 6:298-302.
22. Flokstra-de Blok BM, DunnGalvin A, Vlieg-Boerstra BJ, Oude Elberink JN, Duiverman EJ, Hourihane JO, Dubois AE. Development and validation of the self-administered Food Allergy Quality of Life Questionnaire for adolescents. J Allergy Clin Immunol 2008; 122:139,44, 144.e1-2.
23. Flokstra-de Blok BM, van der Meulen GN, DunnGalvin A et al. . Development and validation of the Food Allergy Quality of Life Questionnaire - Adult Form. Allergy 2009; 64:1209-17.

24. Oude Elberink JN, de Monchy JG, Golden DB, Brouwer JL, Guyatt GH, Dubois AE. Development and validation of a health-related quality-of-life questionnaire in patients with yellow jacket allergy. J Allergy Clin Immunol 2002; 109:162-70.
25. Bullinger M, Anderson R, Cella D, Aaronson N. Developing and evaluating cross-cultural instruments from minimum requirements to optimal models. Qual Life Res 1993; 2:451-9.
26. Boynton PM, Greenhalgh T. Selecting, designing, and developing your questionnaire. BMJ 2004; 328:1312-5.
27. Sampson HA, Munoz-Furlong A, Campbell RL et al. . Second symposium on the definition and management of anaphylaxis: summary report--Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol 2006; 117:391-7.
28. Juniper EF, Guyatt GH, Willan A, Griffith LE. Determining a minimal important change in a disease-specific Quality of Life Questionnaire. J Clin Epidemiol 1994; 47:81-7.
29. Buyan N, Turkmen MA, Bilge I et al. . Quality of life in children with chronic kidney disease (with child and parent assessments). Pediatr Nephrol 2010; 25:1487-96.
30. Guyatt GH, Juniper EF, Griffith LE, Feeny DH, Ferrie PJ. Children and adult perceptions of childhood asthma. Pediatrics 1997; 99:165-8.
31. Annett RD, Bender BG, DuHamel TR, Lapidus J. Factors influencing parent reports on quality of life for children with asthma. J Asthma 2003; 40:577-87.
32. 8ibace R, Wals ME. Developmental stages in children's conceptualizations of illness In: Stone GC, Cohen F, Adler NE, eds. Health Psychology-A Handbook. San Francisco:Jossey-Bass Publishers, 1980:285-301.
33. Koopman HM, Baars RM, Chaplin J, Zwinderman KH. Illness through the eyes of the child: the development of children's understanding of the causes of illness. Patient Educ Couns 2004; 55:363-70.
34. King RM, Knibb RC, Hourihane JO. Impact of peanut allergy on quality of life, stress and anxiety in the family. Allergy 2009; 64:461-8.
35. DunnGalvin A, Hourihane JO, Frewer L, Knibb RC, Oude Elberink JN, Klinge I. Incorporating a gender dimension in food allergy research: a review. Allergy 2006; 61:1336-43.
36. Waters E, Doyle J, Wolfe R, Wright M, Wake M, Salmon L. Influence of parental gender and self-reported health and illness on parent-reported child health. Pediatrics 2000; 106:1422-8.
37. Waters E, Stewart-Brown S, Fitzpatrick R. Agreement between adolescent self-report and parent reports of health and well-being: results of an epidemiological study. Child Care Health Dev 2003; 29:501-9.
38. Kahn RS, Brandt D, Whitaker RC. Combined effect of mothers' and fathers' mental health symptoms on children's behavioral and emotional well-being. Arch Pediatr Adolesc Med 2004; 158:721-9.
39. Gjersing L, Caplehorn JR, Clausen T. Cross-cultural adaptation of research instruments: language, setting, time and statistical considerations. BMC Med Res Methodol 2010; 10:13.
40. Acquadro C, Conway K, Hareendran A, Aaronson N, European Regulatory Issues and Quality of Life Assessment (ERIQA) Group. Literature review of methods to translate health-related quality of life questionnaires for use in multinational clinical trials. Value Health 2008; 11:509-21.
41. Rebok G, Riley A, Forrest C, Starfield B, Green B, Robertson J, Tambor E. Elementary school-aged children's reports of their health: a cognitive interviewing study. Qual Life Res 2001; 10:59-70.
42. Juniper EF, Guyatt GH, Dolovich J. Assessment of quality of life in adolescents with allergic rhinoconjunctivitis: development and testing of a questionnaire for clinical trials. J Allergy Clin Immunol 1994; 93:413-23.
43. Juniper EF, Guyatt GH, Epstein RS, Ferrie PJ, Jaeschke R, Hiller TK. Evaluation of impairment of health related quality of life in asthma: development of a questionnaire for use in clinical trials. Thorax 1992; 47:76-83.
44. Wong SS, Lee BO, Ang RP, Oei TPS, Kwang Ng A. Personality, Health and Coping; A Cross-National Study. Cross-Cultural Res 2009; 43:251-78.
45. Bullinger M, von Mackensen S. Psycho-social determinants of quality of life in children and adolescents with haemophilia-a cross-cultural approach. Clin Psychol Psychother 2008; 15:164-72.
46. Prelow HM, Tein JY, Roosa MW, Wood J. Do coping styles differ across sociocultural groups? The role of measurement equivalence in making this judgment. Am J Community Psychol 2000; 28:225-44.
47. Maramaldi P, Berkman B, Barusch A. Assessment and the ubiquity of culture: threats to validity in measures of health-related quality of life. Health Soc Work 2005; 30:27-38.
48. Cole PM, Bruschi CJ, Tamang BL. Cultural differences in children's emotional reactions to difficult situations. Child Dev 2002; 73:983-96.



Chapter 6

Adolescent-parent disagreement on health-related quality of life of food allergic adolescents; Who makes the difference?

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ABSTRACT

Objective: Food allergic adolescents are at highest risk for food allergy fatalities, which may be partly due to compromised self-management behaviour. Such behaviour may be negatively influenced by conflictual situations caused by adolescent-parent disagreement on the adolescent's Health-Related Quality of Life (HRQL). Comparisons of adolescent-self- and parent-proxy-reported HRQL of food allergic adolescents have never extensively been studied. The aims of this study were to investigate disagreement in adolescent-self- and parent-proxy-reports on the HRQL of food allergic adolescents and to investigate factors influencing adolescent-parent disagreement.

Methods: Teenager Form (-TF) and -Parent Form (-PF) of the Food Allergy Quality of Life Questionnaire (FAQLQ), Food Allergy Independent Measure (FAIM) and Brief-Illness Perception Questionnaire (Brief-IPQ) were sent to Dutch food allergic adolescents (13-17 years) and their parents. ICCs, t-tests and Bland-Altman plots were used to investigate adolescent-parent disagreement. Participant characteristics, illness expectations and perceptions influencing adolescent-parent disagreement were studied (regression analysis).

Results: Seventy adolescent-parent pairs were included. There was a moderate correlation (ICC=0.61, $p<0.001$) and no significant difference (3.78 versus 3.56, $p=0.103$) between adolescent-self and parent-proxy-reported HRQL at group level. However, Bland-Altman plots showed relevant differences (exceeding the minimal important difference) for 63% of all adolescent-parent pairs. Adolescent's age (>15 years), poorer adolescent-reported illness comprehension (Brief-IPQ-TF, coherence) and higher adolescent-reported perceived disease severity (FAIM-TF) were associated with adolescent-parent disagreement.

Conclusions: Adolescent-parent disagreement on the adolescent's HRQL, was mainly associated with adolescents' rather than parents' perceptions and characteristics. Illness comprehension of the adolescent may be an important target for intervention aimed at reducing adolescent-parent disagreement.

INTRODUCTION

Food allergy affects about 2.3% of adolescents[1] and they are at highest risk for food allergy fatalities[2]. This may be caused by the fact that adolescents often engage in risk-taking behaviors[2-4] resulting in reduced vigilance about food consumption or reluctance to carry the epinephrine auto-injector (EAI)[4-6]. Such compromised self-management behaviour may be exacerbated by parent-patient conflicts on the adolescent's Health-Related Quality of Life (HRQL). For example, parents may not recognize the social impact of food avoidance and carrying an EAI on their adolescent's HRQL. However, these and other aspects of the adolescent's HRQL[7-12] may be considered as problematic by adolescents themselves and this may cause parent-patient conflicts. Relationships between reduced disease management and family conflict have previously been shown in adolescents with diabetes[13]. Additionally, interventions reducing family conflict were associated with better blood glucose monitoring[14,15] and HRQL[16]. Therefore, it is important to study adolescent-parent disagreement on the adolescent's HRQL in food allergy as well. Another reason for studying parent-reports in addition to adolescent-self-reports on the adolescent's HRQL is the fact that parental attitudes may influence adolescents' own attitudes[17]. For example, parental anxiety on vigilance about food consumption may serve as a psychosocial stressor for the adolescent. Additionally, parental attitudes, beliefs and fears can have an impact on the utilization of health care services for their child[18] and parents may provide information not provided by adolescents themselves[19].

A number of factors may predict adolescent-parent disagreement on the adolescent's HRQL[20-22], including socio-demographic variables, illness perceptions, expectations and anxiety. For example, adolescents who report low risk perception scores on illness-expectation-questions such as "how big do you think the chance is of dying because of your food allergy?" may report better HRQL than parents reporting high risk perception. Consequently, this may cause adolescent-parent disagreement on the adolescent's HRQL. However, research findings remain inconclusive regarding the effects of these variables[20-22]. Moreover, these variables have not been studied in food allergic adolescents (13-17 years).

Therefore, the aims of this study were to compare adolescent-self and parent-reports on the HRQL of food allergic adolescents and secondly, to investigate variables that may influence adolescent-parent disagreement on the adolescent's HRQL to identify potential targets for interventions aimed at reducing such disagreement.

METHODS

Participants and procedures

Dutch food allergic adolescents (13-17 years) and their parents were recruited from the paediatric allergy clinic or through Dutch food allergy support organizations[10] between

May and July 2010. Adolescents with at least one physician diagnosed food allergy were included. Possible differences between descriptive characteristics (Table 1) of adolescent-parent pairs recruited by clinic and advertisement were examined using Chi-square-test (nominal/ordinal data) and Mann-Whitney-test (numeric data).

Questionnaire-packages and a letter of invitation were sent by mail to be completed at home. Adolescent-parent pairs were instructed that they were not allowed to discuss questions with each other. Participation in the study was completely voluntary. This study was approved by the local medical ethics review commission who deemed that formal approval by the commission was not required (METc 2005/051).

Questionnaires

Food Allergy Quality of Life Questionnaire-Teenager Form (FAQLQ-TF)

The original Dutch FAQLQ-TF is a adolescent-self-report instrument for measuring the impact of food allergy on the adolescent's HRQL[10]. The FAQLQ-TF contains 23 items and 3 domains (Allergen Avoidance & Dietary Restrictions, Risk of Accidental Exposure and Emotional Impact). Items are scored on a seven-point scale. Total FAQLQ score is the sum of all items divided by the number of items and ranges from 1 (minimal impairment of HRQL) to 7 (maximal impairment of HRQL).

Food Allergy Quality of Life Questionnaire-Parent Form, Adolescent version (FAQLQ-PFA)

The original English FAQLQ-PFA is a parent-proxy-report instrument for measuring the impact of food allergy on the adolescent's HRQL[23,24], appendix 1. The FAQLQ-PFA was translated into Dutch using the guidelines of the World Health Organization. Two native Dutch speakers translated the FAQLQ-PFA from English into Dutch and two native English speakers translated the Dutch FAQLQ-PFA back into English. The original English version was compared with the back-translated English version by an expert panel. No important differences in content or meaning of questions emerged during translation and pre-testing. The FAQLQ-PFA contains 27 items and 4 domains (Emotional Impact, Food Anxiety, Social restrictions and Dietary restrictions). Items are scored in the same way as the FAQLQ-TF.

Food Allergy Independent Measure-Teenager Form & -Parent Form (FAIM-TF & -PF)

The FAIM reflects the participant's perceived disease severity and their food allergy-related risk perception. The Dutch FAIM was originally developed as an independent measure for food allergy[25] to evaluate the construct validity of the FAQLQs. The FAIM-TF (adolescent-self-report) and -PF (parent-proxy-report) contain four expectations of outcome questions, which capture the patients' perceived expectation of the chance of accidental exposure and of what will happen following accidental exposure and two questions reflecting

disease severity. Each question was scored on a scale ranging from 1 (no chance) to 7 (certainty). Total FAIM score is the sum of all items divided by the number of items.

Brief-Illness Perception Questionnaire-Teenager Form & -Parent-proxy Form (Brief-IPQ-TF & -PF)

The Brief-IPQ contains five items reflecting cognitive illness representations, two items reflecting emotional illness representations and two items reflecting coherence (illness comprehension, i.e. the adolescent's perceived understanding of food allergy) and causal illness representation. Items are scored on a scale ranging from 1 (benign view of illness) to 11 (threatening view of illness), except for the open-ended causal item. The New Zealand's Brief-IPQ[26] was previously validated in the Netherlands[27].

Descriptive characteristics

Additional questions on food allergy, socio-demographic parameters and trait anxiety were administered. The trait anxiety scale of the State and Trait Anxiety Inventory (STAI) was used as an anxiety measure[28,29] and was completed as a self-report by adolescent and parents. The scale contains 20 items, which are scored on a scale ranging from 1 (no anxiety) to 3 (severe anxiety) for adolescents and from 1 to 4 for adults.

Statistical analysis

Adolescent-parent disagreement

Comparison of outcome

Data were analyzed using SPSS software for Windows (Version 16.0). Three methods were used to investigate adolescent-parent disagreement to provide sufficient information on such disagreement. Firstly, total FAQLQ-TF and FAQLQ-PFA scores were tested for significant differences (paired-sampled t-test). $P<0.05$ was considered to be significant. Secondly, total FAQLQ-TF and FAQLQ-PFA scores were correlated using intraclass correlation coefficients (ICC, two-way mixed-effects model). Thirdly, Bland-Altman plots were used to visualize the differences between FAQLQ-TF and -PF scores for individual adolescent-parent pairs. Therefore, the mean FAQLQ score of each adolescent-parent pair was plotted against the difference (FAQLQ-TF minus FAQLQ-PFA score) of each adolescent-parent pair. As it is important to know whether a difference between FAQLQ-TF and -PFA scores is clinically meaningful for patients, the minimal important difference (MID) was used to calculate the percentage of individual adolescent-parent pairs reporting clinically relevant differences exceeding the MID. The MID reflects the smallest difference or change in HRQL score associated with a difference or change in health status that patients find meaningful. In HRQL questionnaires with a seven-point scale the MID is usually around 0.5[30]. The mean difference +/- the MID (0.5) was used as limits of agreement. The same procedure was followed for comparisons between FAIM-TF and -PF and between Brief-IPQ-TF and -PF.

Comparison of measurement properties

Construct validity of the FAQLQs was investigated calculating Pearson's correlation coefficient between FAQLQ-PFA and FAIM-PF scores and between FAQLQ-TF and FAIM-TF scores, respectively. Moderate correlations (0.40-0.60) were expected[31]. Internal consistency was investigated using Cronbach's alpha ($\alpha \geq 0.70$ was considered to be good). Discriminative abilities were investigated comparing total questionnaire scores for boys versus girls, for adolescents who have two or less versus more than two food allergies (independent-samples T-tests) and for adolescents who experienced anaphylaxis[32] versus adolescents who did not (Mann-Whitney U-test). Floor and ceiling effects were calculated as percentage of patients with lowest and highest total questionnaire scores, respectively.

Factors influencing adolescent-parent disagreement on HRQL

Univariate and adjusted linear regression analyses were performed to investigate factors influencing adolescent-parent disagreement. The mean difference between adolescent- and parent-reported HRQL (FAQLQ-TF minus FAQLQ-PFA score) was used as outcome variable and participant characteristics (table 1), illness expectations (FAIM) and perceptions (Brief-IPQ) were used as predictor variables. Predictor variables were entered into the adjusted linear regression model (enter procedure) when they were associated with the outcome variable in the univariate regression analysis ($p<0.05$). There was multicolinearity (Pearson>0.60) for the variables Brief-IPQ-TF and FAIM-TF. Therefore, variable Brief-IPQ-TF was deleted from the adjusted model and replaced by domain coherence, which was not associated with FAIM-TF.

RESULTS

Participants

Questionnaire-packages were sent to 122 adolescent-parent pairs and returned by 74 adolescent-parent pairs. One adolescent-parent pair was excluded, because the adolescent had outgrown his food allergy. Three adolescent-parent pairs were excluded because less than 85% of the questions were completed. Therefore, 70 adolescent-parent pairs were eligible for analysis.

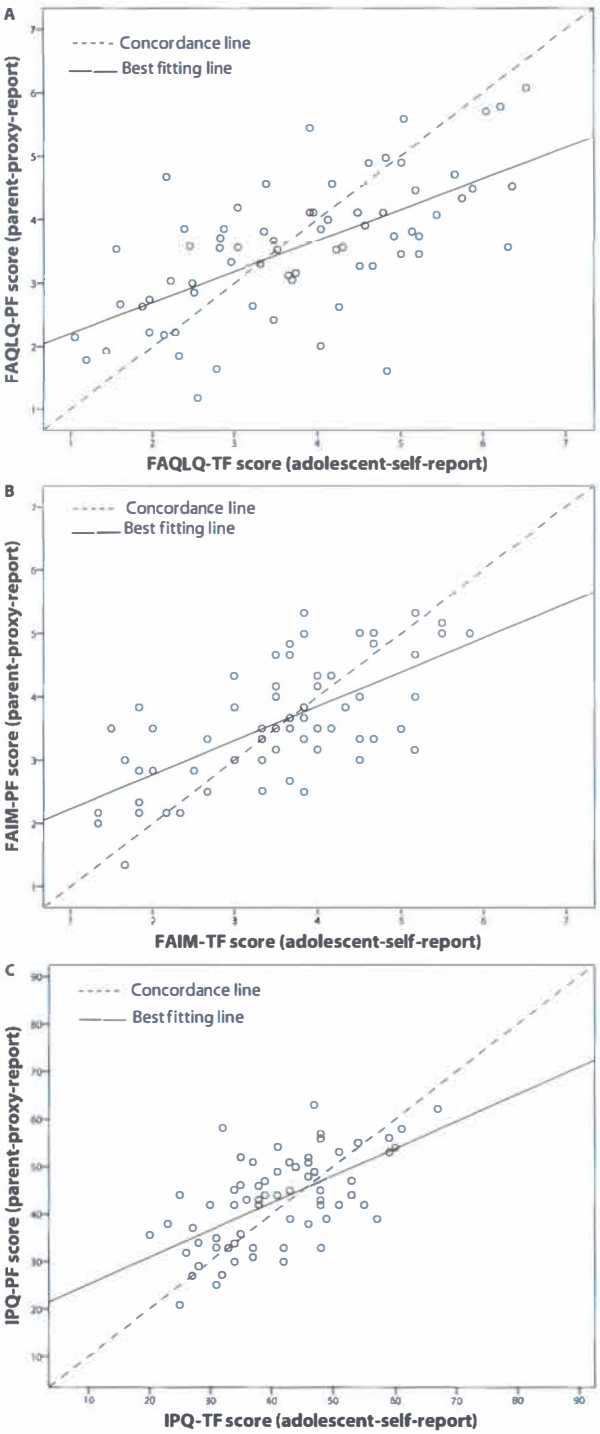
Table 1 shows the descriptive characteristics. Forty-eight adolescent-parent pairs were recruited from our clinic, of whom 31 had a food allergy confirmed by a double-blind placebo-controlled food challenge (DBPCFC), two by an open food challenge and fifteen by skin prick test, blood test or both. Twenty-two adolescent-parent pairs were recruited by advertisement and all reported physician-diagnosed food allergies. There were no significant differences in descriptive characteristics (Table 1) between adolescents recruited from clinic and advertisement (p-values ranged from 0.052 [presence of sesame allergy] to 0.946 [presence of vegetable allergy]) or between adolescents diagnosed by means of a DBPCFC and otherwise diagnosed.

Table 1. Descriptive characteristics adolescent-parent pairs

Number adolescent-parent pairs, n	70	
Sex adolescent, girls/boys	30 / 40	
Mean age adolescent, years (SD)	15.3 (1.2)	
Type of food allergies adolescent, n		
Peanut	52	
Nut	52	
Milk	18	
Egg	14	
Wheat	5	
Soy	12	
Sesame	6	
Fish	2	
Shell fish	7	
Fruit	18	
Vegetables	6	
Number of food allergies adolescent, n		
1 food	14	
2 foods	23	
3 foods	17	
> 3 foods	16	
Most severe symptoms adolescent, n		
Cardiovascular	33	
Respiratory	27	
Gastro-intestinal	4	
Skin and other[1]	5	
Anaphylaxis adolescent, yes/no	52/17	
Last experience of anaphylaxis, years (SD)	5.2 (4.5)	
Trait-anxiety adolescent, score (SD)		
Boys [norm data boys]	28.5 (5.6)	[28.7 (6.4)]
Girls [norm data girls]	31.1 (7.4)	[32.5 (6.6)]
Atopic comorbidities adolescent		
Asthma	42	
Eczema	31	
Allergic rhinitis	42	
Parental sex, male/female	8 / 62	
Parental age, years (SD)	47.6 (3.9)	
Parental marital status, n		
Married/ Living together	62	
Divorced/ Living alone	8	
Parental workforce participation, yes/no	53/17	
Parental educational level, n		
High school	3	
Vocational education	23	
Professional education	35	
University degree	9	
Parental trait-anxiety, score (SD)		
Male	28.5 (5.6)	
Female	31.1 (7.4)	
Norm Data	32.8 (8.3)	
Family income, n		
(missing data)	(12)	
< Middle income[2]	3	
Middle income	9	
> Middle income	46	

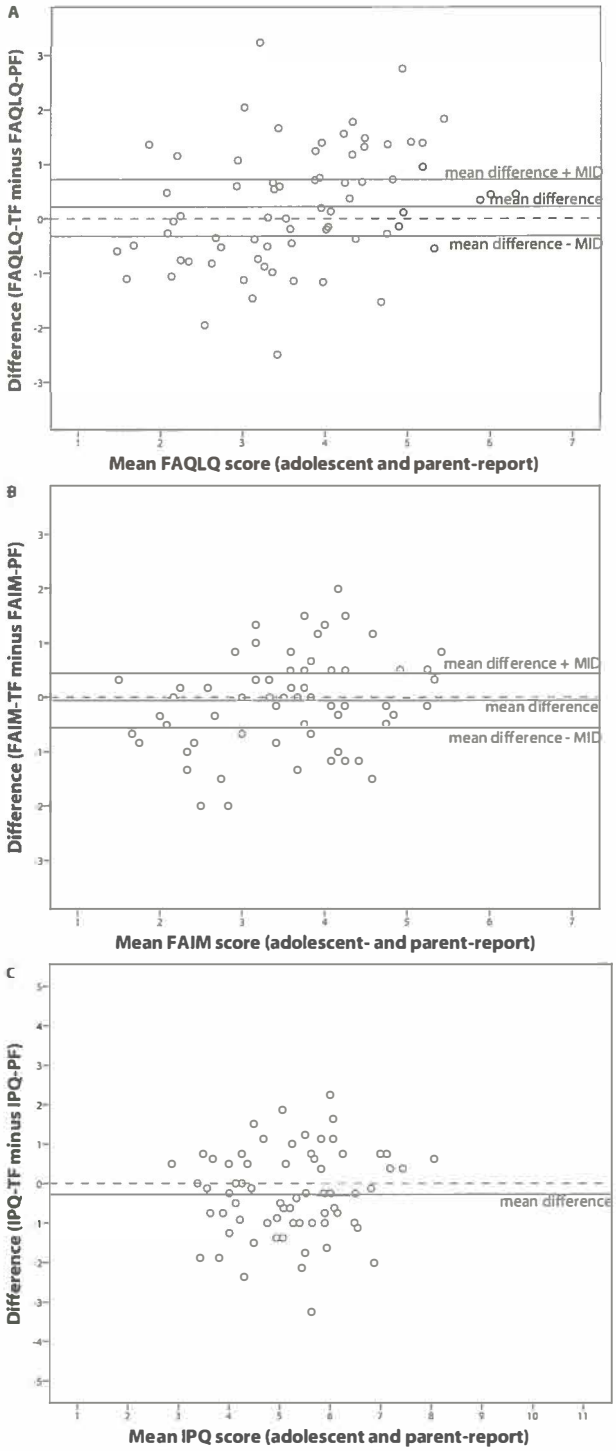
1 Oral allergy symptoms, nose/eye symptoms etc
2 Based on calculations Dutch Central Planning Agency

Figure 1. Adolescent-self-reports versus parent-proxy-reports for (A) health-related quality of life (B) perceived disease severity (C) illness perceptions



FAIM = Food Allergy Independent Measure Questionnaire. FAQLQ = Food Allergy Quality of Life Questionnaire. IPQ = Illness Perception Questionnaire.

Figure 2. Bland Altman plots illustrating adolescent-parent agreement for (A) food allergy-related quality of life (B) perceived disease severity (C) illness perceptions



FAIM = Food Allergy Independent Measure Questionnaire. FAQLQ = Food Allergy Quality of Life Questionnaire. IPQ = Illness Perception Questionnaire. MID = Minimal clinically Important Difference of HRQL instruments using a 7-point scale.

Table 2. Comparison of outcome of adolescent- and parent-reports on health-related quality of life (FAQLQ), illness expectations (FAIM) and perceptions (IPQ)

	Outcome adolescent-report Score (SD)		**Outcome parent-report** Score (SD)		**Correlation adolescent- parent reports** ICC
FAQLQ, total score	3.78	(1.39)	3.56	(1.07)	**0.61**
Allergen avoidance & Dietary Restrictions	3.88	(1.46)			
Risk of accidental Exposure	3.67	(1.59)			
Emotional impact	3.71	(1.57)			
Dietary Restrictions			4.18	(1.37)	
Food anxiety			3.82	(1.14)	
Social Restrictions			3.21	(1.32)	
Emotional impact			3.09	(1.16)	
FAIM (illness expectations), total score	3.55	(1.10)	3.61	(0.90)	**0.64**
Chance of accidental exposure	3.54	(1.20)	3.36	(1.06)	**0.34**
Chance of severe reaction	4.57	(1.80)	4.63	(1.66)	**0.33**
Chance of dying following exposure	2.86	(1.60)	2.97	(1.55)	**0.57**
Chance of not dealing with a reaction	3.19	(1.40)	3.23	(1.31)	**0.36**
Number of products to avoid	4.16	(1.52)	4.23	(1.12)	**0.70**
Impact on social life	2.99	(1.62)	3.23	(1.45)	**0.69**
Brief-IPQ (illness perceptions), total score	**5.04**	**(1.31)**	**5.32**	**(1.19)**	**0.63**
Consequences	5.77	(2.70)	5.96	(2.34)	**0.60**
Timeline	9.84	(2.26)	10.20	(1.95)	**0.63**
Personal control	3.51	(2.27)	3.12	(1.98)	**0.40**
Treatment control	6.31	(2.60)	6.37	(2.93)	**0.28**
Identity	4.81	(3.13)	5.29	(2.98)	**0.45**
Illness concern	**4.36**	**(3.11)**	**5.14**	**(2.70)**	**0.52**
Coherence (illness comprehension)	2.56	(1.71)	2.31	(1.57)	**0.25**
Emotional representations	**3.17**	**(2.63)**	**4.14**	**(2.54)**	**0.51**
Open ended question: Main cause of food allergy (Top 5)	n	(%)	n	(%)	**0.31**
No idea	26	(38)	15	(22)	
Genetic/ Innate	29	(42)	34	(49)	
Environmental factors	6	(9)	5	(7)	
Dysfunction of immune system	3	(4)	3	(4)	
Coincidence/ bad luck	2	(3)	5	(7)	
Other[1]	4	(6)	8	(11)	

1 Hygiene in Western Europe, combination with other atopic disorders, food industry etc.
Scores in **boldface** represent significant values ($P < 0.05$).

Comparison FAQLQ-TF and FAQLQ-PFA

There was no significant difference between FAQLQ-TF and FAQLQ-PFA total scores (3.78 versus 3.56, p=0.103, df = 69) and the correlation between them was good (Table 2, Figure 1A). The Bland-Altman plot illustrates that 63% of the differences between adolescent- and parent-reported HRQL of all individual adolescent-parent pairs exceeded the limits of agreement reflecting the mean difference +/- the minimal clinically important difference (Figure 2A), i.e. 63% of all adolescent-parent pairs reported clinically relevant differences in the adolescent's HRQL.

Measurement properties of the FAQLQ-TF and -PFA were considered to be good (Table 3).

Comparison FAIM-TF and -PF

There was no significant difference between adolescent- and parent-reported total FAIM scores (3.55 versus 3.61, p=0.574) or between individual item scores (Table 2). There was a good correlation between adolescent- and parent-reported total FAIM scores (Figure 1B), and for the items "number of products to avoid" and "impact on social life". There were moderate to poor correlations between adolescent- and parent-reports for the other items (Table 2). The Bland-Altman plot illustrates that 53% of all adolescent-parent pairs showed differences between adolescent- and parent-reported FAIM scores which exceeded the MID (Figure 2B).

Measurement properties of the FAIM-TF and -PF were considered to be good (Table 3).

Comparison brief-IPQ-TF and -PF

There was a significant difference between adolescent-self and parent-proxy-reported IPQ total scores (5.04 versus 5.32, p=0.037), item 'illness concern" (4.36 versus 5.14, p=0.024) and item "emotional representations" (3.17 versus 4.14, p=0.002) (Table 2). The differences for the items exceeded the smallest detectable change (SDC)[27]. In other words, parents reported more emotions and concerns about food allergy than adolescents themselves. There was a good correlation between adolescent- and parent-reported total brief-IPQ scores (Figure 1C). Items "treatment control" and "coherence" showed poor correlations (Table 2). The Bland-Altman plot illustrates that relevant differences were shown for some adolescent-parent pairs (Figure 2C).

Measurement properties of the brief-IPQ-TF and -PF were considered to be moderate to good (Table 3).

Factors influencing adolescent-parent disagreement on HRQL

The final adjusted model explained 40.7% of variance in the difference between adolescent- and parent-reported HRQL (p<0.001); i.e. increased age of the adolescent (16-17 years), higher perceived disease severity (FAIM-TF) and poorer adolescent-reported perceived illness comprehension (coherence) all contributed significantly to a

larger difference between adolescent- and parent-reported HRQL (Table 4). There was borderline significance for the association between last experience of anaphylaxis and the difference between adolescent- and parent-reported HRQL; i.e. a more recent diagnosis of food allergy causes a larger difference between adolescent- and parent-reported HRQL. The effect of parental workforce was confounded by the variables adolescent coherence and age.

Interestingly, adolescent-reported illness perceptions and expectations showed stronger associations with the mean difference on HRQL than parent-reported illness perceptions and expectations.

Table 3. Comparison of measurement properties of the Food Allergy Quality of Life Questionnaires, (FAQLQ), Food Allergy Independent Measure (FAIM) and Illness Perception Questionnaire (IPQ)

	Validity	**Internal Consistency**	**Floor & Ceiling effects**[1]	**Discriminative abilities**		
				Sex	**Number food allergies**	**Anaphylaxis**
	Pearson	α	% / %	boys vs girls	≤2 vs >2	no vs yes
FAQLQ-TF	0.77	0.96	0 / 0	3.58vs 4.04 (p=0.167)	3.52 vs 4.06 (p=0.110)	3.14 vs 4.03 **(p=0.023)**
AADR	0.61	0.93	1.4 / 1.4	n.p.[2]	n.p.	n.p.
RAE	0.74	0.85	2.9 / 1.4	n.p.	n.p.	n.p.
EI	0.66	0.89	1.4 / 1.4	n.p.	n.p.	n.p.
FAQLQ-PFA	0.64	0.94	0 / 0	3.36 vs 3.83	3.42 vs 4.04 **(p=0.039)**[3]	2.88 vs 3.79 **(p=0.004)**
DR	0.58	0.89	0 / 0	n.p.	n.p.	n.p.
FA	0.53	0.77	0 / 0	n.p.	n.p.	n.p.
SR	0.44	0.82	2.9 / 1.4	n.p.	n.p.	n.p.
EI	0.61	0.84	1.4 / 0	n.p.	n.p.	n.p.
FAIM-TF	n.a.[4]	0.81	0 / 0	3.44 vs 3.69 (p=0.343)	3.24vs 3.90 **(p=0.011)**	3.01 vs 3.75 **(p=0.029)**
FAIM-PF	n.a.	0.73	0 / 0	3.50 vs 3.74 (p=0.273)	3.42 vs 3.82 (p=0.064)	3.15 vs 3.77 **(p=0.016)**
Brief-IPQ-TF	n.a.	0.59	0 / 0	4.83 vs 5.35 (p=0.100)	4.79 vs 5.30 (p=0.108)	4.79 vs 5.17 (p=0.343)
Brief-IPQ-PF	n.a.	0.66	0 / 0	5.06 vs 5.69 **(p=0.027)**	4.99 vs 5.65 **(p=0.013)**	4.93 vs 5.46 (p=0.079)

1 Percentage of patients with the minimal (floor) or maximal (ceiling) questionnaire score.
2 n.p. not performed
3 The FAQLQ-PF discriminated between adolescents with ≤3 food allergies versus >3 food allergies
4 n.a. not applicable.

Table 4. Univariate & adjusted associated factors influencing adolescent-parent agreement on HRQL

	Univariate associations				Adjusted associations		
	B	R^2 (%)	P	CI	B	P	CI
Adolescent characteristics							
Sex (girls versus boys)	-0.002	0.0	0.995	-0.532 – 0.529			
Age (13-15 versus 16-17 years)	0.710	9.2	**0.011**	0.171 – 1.249	0.823	0.001	0.332 – 1.314
Number food allergies (0-2 versus >2)	0.153	0.5	0.562	-0.372 – 0.678			
Anaphylaxis (no versus yes)	-0.028	0.0	0.926	-0.628 – 0.572			
Last experience of anaphylaxis (how long ago in years)	-0.073	9.3	**0.011**	-0.129 – -0.018	-0.049	0.052	-0.098 – 0.000
Anxiety (STAI-TF)	0.017	2.9	0.161	-0.007 – 0.040			
Adolescent-reported perceived disease severity (FAIM-TF)	0.365	13.4	**0.002**	0.140 – 0.590	0.216	0.040	0.010 - 0.422
Adolescent-reported illness perceptions (IPQ-TF)	0.413	24.3	**<0.001**	0.235 – 0.592			
Coherence (illness comprehension)	0.230	12.9	**0.002**	0.084 – 0.375	0.229	0.002	0.091 – 0.367
Emotional perceptions	0.182	18.7	**<0.001**	0.090 – 0.275			
Cognitive perceptions	0.309	12.8	**0.003**	0.112 – 0.505			
Parent characteristics							
Sex (female versus male)	-0.013	0.0	0.977	-0.888 – 0.862			
Age (years)	-0.020	0.5	0.561	-0.088 – 0.048			
Marital status (together versus alone)	0.136	0.2	0.742	-0.688 – 0.961			
Workforce participation (no versus yes)	0.628	6.2	**0.038**	0.035 - 1.221	0.203	0.447	-0.327 – 0.732
Education (≤ vocational versus > vocational)	-0.116	0.3	0.676	-0.669 – 0.437			
Anxiety (STAI-PF)	0.026	2.9	0.162	-0.011 – 0.063			
Family income (≤ middle versus > middle)	0.266	1.0	0.461	-0.451 – 0.983			
Parent-reported perceived disease severity (FAIM-PF)	0.047	0.2	0.750	-0.246 – 0.340			
Parent-reported illness perceptions (IPQ-PF)	0.067	0.6	0.539	-0.149 - 0.283			
Coherence (illness comprehension)	-0.032	0.3	0.680	-0.188 – 0.123			
Emotional representations	0.028	0.4	0.615	-0.081 – 0.137			
Cognitive representations	0.080	0.7	0.477	-0.144 – 0.304			

Scores in **boldface** represent significant values (P < 0.05).

DISCUSSION

This is the first study comparing self- and parent-reports on the adolescent's HRQL in food allergic adolescents using valid and disease-specific HRQL-instruments. Although substantial correlations and no significant differences were shown between adolescent-self and parent-proxy-reported HRQL on a group level, there was a clinically important difference in HRQL scores (i.e. exceeding the minimal important difference) for 63% of all individual adolescent-parent pairs; i.e. 63% of all individual adolescent-parent pairs reported clinically relevant differences in the adolescent's HRQL. As the minimal important difference reflects the smallest difference in HRQL score associated with a difference in health status that patients find meaningful, this is a very important parameter in interpreting our study results. Clinicians should thus be aware of disagreement in perspectives on the adolescent's HRQL and the factors contributing to such disagreement.

Several factors were associated with adolescent-parent disagreement on the adolescent's HRQL. It was quite revealing that the adolescent's characteristics (age, last experience of anaphylaxis), illness perceptions and expectations (table 4) had much stronger associations with the mean difference on the adolescent's HRQL than parent-proxy perceptions and expectations. In other words, a high subjective disease severity (amount of products to avoid, chance of severe reaction following exposure, etc.) and worse subjective illness comprehension (perceived understanding food allergy) as perceived by the adolescent caused larger differences between adolescent- and parent-reported HRQL, whereas the same perceptions as perceived by the parent were not associated with the difference between adolescent- and parent-reported HRQL. This suggests that adolescents mainly determine adolescent-parent disagreement on the adolescent's HRQL, because most determinants of the adolescent's HRQL are poorly perceived by their parents.

Additionally, adolescent's age was associated with adolescent-parent disagreement on the adolescent's HRQL. We found better adolescent-parent agreement for younger (13-15 years) than for older adolescents (16-17 years). Associations between age and child-parent agreement on HRQL have been previously shown[33-35]. We previously studied food allergic children aged 8-12 years[35] and reported better child-parent agreement for older (11-12 years) than for younger children (8-10 years). This may be caused by the fact that as children mature they become more articulate in expressing their feelings or concerns and consequently, parents may have a better insight into their child's HRQL. The age-effect in the current study may be caused by the fact that as adolescents mature, they spend less time under parental supervision and develop their independence. Consequently, older adolescents may be less influenced by their parents and parents may have less insight into their older adolescent's HRQL. These factors may negatively influence adolescent-parent agreement. It thus seems likely that child-parent agreement on the impact of food allergy on the child's HRQL is associated with age and that child-parent agreement is highest for food allergic children aged 11-15 years.

As it was previously shown that family conflict negatively impacts on self-management behavior of diabetic adolescents[14,15], it is possible that adolescent-parent disagreement on the adolescent's HRQL may influence self-management behavior of food allergic adolescents as well. As poorer adolescent-reported illness comprehension was associated with adolescent-parent disagreement, this may be a target for intervention aimed at reducing disagreement. The impact of illness comprehension on adolescent-parent disagreement may also be reflected by the fact that a less recent diagnosis of food allergy (last experience of anaphylaxis) was associated with better adolescent-parent agreement. Adolescents with a less recent diagnosis of food allergy and their parents have probably visited clinicians more often and may have improved their comprehension of food allergy resulting in better adolescent-parent agreement on HRQL. Although the relationship between adolescent-parent disagreement on the adolescent's HRQL and self-management behavior is hypothetical in food allergy, illness comprehension of the adolescent may be an important target for intervention aimed at reducing disagreement. Future studies might focus on education programs for adolescents able to improve their understanding of food allergy. Such programs may also reduce adolescent-parent disagreement and improve self-management.

Our results provide insight into several determinants of adolescent-parent disagreement on the adolescent's HRQL. As 59.3% of the variance in the difference between self and parent-proxy-reports on the adolescent's HRQL has not been explained yet, further research may identify additional variables influencing adolescent-parent disagreement. Parental gender may be such a variable. In our study, the FAQLQ-PFA was mainly completed by mothers. As fathers may have a different view on their adolescent's HRQL than mothers, this may influence adolescent-parent disagreement.

There is no consensus in literature on whether parents systematically report poorer or better HRQL than their child[20,22,35-37]. These differences in results may depend on several factors such as the disease studied, the instruments used, the age of the child and culture. However, there is consensus on the fact that there generally is moderate child-parent agreement on the child's HRQL. Therefore, it is important to recognize the fact that there is disagreement and to discuss areas, determinants and possible consequences of disagreement with child-parent pairs.

In summary, the FAQLQ-TF and -PFA should be used together to highlight areas of adolescent-parent disagreement which require special attention. There is moderate adolescent-parent agreement on the adolescent's HRQL. Disagreement is determined mainly by the adolescent's characteristics and perceptions of food allergy rather than the parent's perceptions and characteristics. Illness comprehension of the adolescent may be an important target for intervention aimed at reducing adolescent-parent disagreement on the adolescent's HRQL.

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REFERENCE LIST

1. Pereira B, Venter C, Grundy J, Clayton CB, Arshad SH, Dean T. Prevalence of sensitization to food allergens, reported adverse reaction to foods, food avoidance, and food hypersensitivity among teenagers. J Allergy Clin Immunol 2005; 116:884-92.
2. Mackenzie H, Roberts G, van Laar D, Dean T. Teenagers' experiences of living with food hypersensitivity: A qualitative study. Pediatr Allergy Immunol 2010; 21(4 Pt 1):595-602
3. Sampson MA, Munoz-Furlong A, Sicherer SH. Risk-taking and coping strategies of adolescents and young adults with food allergy. J Allergy Clin Immunol 2006; 117:1440-5.
4. Monks H, Gowland MH, Mackenzie H, et al. How do teenagers manage their food allergies? Clin Exp Allergy 2010; 40:1533-40.
5. Akeson N, Worth A, Sheikh A. The psychosocial impact of anaphylaxis on young people and their parents. Clin Exp Allergy 2007; 37:1213-20.
6. Cummings AJ, Knibb RC, Erlewyn-Lajeunesse M, King RM, Roberts G, Lucas JS. Management of nut allergy influences quality of life and anxiety in children and their mothers. Pediatr Allergy Immunol 2010; 21(4 Pt 1):586-94.
7. Lebovidge JS, Strauch H, Kalish LA, Schneider LC. Assessment of psychological distress among children and adolescents with food allergy. J Allergy Clin Immunol 2009; 124:1282-8.
8. Marklund B, Wilde-Larsson B, Ahlstedt S, Nordstrom G. Adolescents' experiences of being food-hypersensitive: A qualitative study. BMC Nurs 2007;6:8.
9. Cummings AJ, Knibb RC, King RM, Lucas JS. The psychosocial impact of food allergy and food hypersensitivity in children, adolescents and their families: A review. Allergy 2010; 65:933-45.
10. Flokstra-de Blok BM, DunnGalvin A, Vlieg-Boerstra BJ, et al. Development and validation of the self-administered food allergy quality of life questionnaire for adolescents. J Allergy Clin Immunol 2008; 122:139,44, 144.e1-2.
11. Lyons AC, Forde EM. Food allergy in young adults: Perceptions and psychological effects. J Health Psychol 2004; 9:497-504.
12. Resnick ES, Pieretti MM, Maloney J, Noone S, Munoz-Furlong A, Sicherer SH. Development of a questionnaire to measure quality of life in adolescents with food allergy: The FAQL-teen. Ann Allergy Asthma Immunol 2010; 105:364-8.
13. Anderson BJ, Vangsness L, Connell A, Butler D, Goebel-Fabbri A, Laffel LM. Family conflict, adherence, and glycaemic control in youth with short duration type 1 diabetes. Diabet Med 2002; 19:635-42.
14. Ingerski LM, Anderson BJ, Dolan LM, Hood KK. Blood glucose monitoring and glycemic control in adolescence: Contribution of diabetes-specific responsibility and family conflict. J Adolesc Health 2010; 47:191-7.
15. Anderson BJ, Brackett J, Ho J, Laffel LM. An office-based intervention to maintain parent-adolescent teamwork in diabetes management. impact on parent involvement, family conflict, and subsequent glycemic control. Diabetes Care 1999; 22:713-21.
16. Weissberg-Benchell J, Nansel T, Holmbeck G, e tal. Generic and diabetes-specific parent-child behaviors and quality of life among youth with type 1 diabetes. J Pediatr Psychol 2009; 34:977-88.
17. Kahn RS, Brandt D, Whitaker RC. Combined effect of mothers' and fathers' mental health symptoms on children's behavioral and emotional well-being. Arch Pediatr Adolesc Med 2004; 158:721-9.
18. Upton P, Lawford J, Eiser C. Parent-child agreement across child health-related quality of life instruments: A review of the literature. Qual Life Res 2008; 17:895-913.
19. Eiser C, Morse R. Quality-of-life measures in chronic diseases of childhood. Health Technol Assess 2001; 5:1-157.
20. Waters E, Stewart-Brown S, Fitzpatrick R. Agreement between adolescent self-report and parent reports of health and well-being: Results of an epidemiological study. Child Care Health Dev 2003; 29:501-9.
21. Eiser C, Morse R. Can parents rate their child's health-related quality of life? results of a systematic review. Qual Life Res 2001; 10:347-57.
22. Davis E, Nicolas C, Waters E, et al. Parent-proxy and child self-reported health-related quality of life: Using qualitative methods to explain the discordance. Qual Life Res 2007; 16:863-71.
23. Hamp N, Hourihane J, Knibb RC, Dubois AE, Flokstra-de Blok BM, DunnGalvin A. Developmental specificity and sensitivity between two age appropriate health-related quality of life measures in food allergic children and teenagers. J Allergy Clin Immunol 2008; 121:S107.

24. Hamp A, Knibb RC, van der Velde JL, Flokstra-de Blok BMJ, Dubois AEJ. Development and validation of a parent-administered food allergy quality of life questionnaire for adolescents. 2011; submitted manuscript.
25. van der Velde JL, Flokstra-de Blok BM, Vlieg-Boerstra BJ, et al. Development, validity and reliability of the food allergy independent measure (FAIM). Allergy 2010; 65:630-5.
26. Broadbent E, Petrie KJ, Main J, Weinman J. The brief illness perception questionnaire. J Psychosom Res 2006; 60:631-7.
27. Master thesis. patient's illness perception: An additional part of pyshiotherapy assessment. cross-cultural adaptation and measurement properties of the brief illness perception questionnaire-dutch language version [homepage on the Internet]. http://www.edwinderaaij.nl/downloads/UU/master_thesis_edwin_de_raaij.pdf: 2007.
28. Spielberger CD, Gorsuch RL, Lushene R, Jacobs GA, editors. Manual for the state-trait anxiety inventory (STAI). PaloAlto, CA: Consulting Psychologists Press; 1984.
29. Ploeg van der HM. De zelf-beoordelings vragenlijst (STAI-DY). de ontwikkkeling en validatie van een nederlandstalige vragenlijst voor het meten van angst. Tijdschrift voor psychiatrie 1982; 9:576-88.
30. Juniper EF, Guyatt GH, Willan A, Griffith LE. Determining a minimal important change in a disease-specific quality of life questionnaire. J Clin Epidemiol 1994; 47:81-7.
31. Bullinger M, Anderson R, Cella D, Aaronson N. Developing and evaluating cross-cultural instruments from minimum requirements to optimal models. Qual Life Res 1993; 2:451-9.
32. Sampson HA, Munoz-Furlong A, Campbell RL, et al. Second symposium on the definition and management of anaphylaxis: Summary report--second national institute of allergy and infectious Disease/Food allergy and anaphylaxis network symposium. J Allergy Clin Immunol 2006; 117:391-7.
33. Annett RD, Bender BG, DuHamel TR, Lapidus J. Factors influencing parent reports on quality of life for children with asthma. J Asthma 2003; 40:577-87.
34. Guyatt GH, Juniper EF, Griffith LE, Feeny DH, Ferrie PJ. Children and adult perceptions of childhood asthma. Pediatrics 1997; 99:165-8.
35. van der Velde JL, Flokstra-de Blok BM, DunnGalvin A, Hourihane JO, Duiverman EJ, Dubois AE. Parents report better food allergy-related quality of life for their food allergic children (8-12 years) than children themselves. Clin Exp Allergy 2011; 41:1431-39.
36. King RM, Knibb RC, Hourihane JO. Impact of peanut allergy on quality of life, stress and anxiety in the family. Allergy 2009; 64:461-8.
37. White-Koning M, Arnaud C, Dickinson HO, et al. Determinants of child-parent agreement in quality-of-life reports: A European study of children with cerebral palsy. Pediatrics 2007; 120:e804-14.

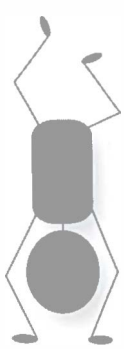
APPENDIX 1

Food Allergy Quality of Life Questionnaire-Parent Form-Adolescents aged 13-17 years (FAQLQ-PFA)

Instructions for participants: The following are all scenarios that parents have told us affect their adolescent's quality of life because of food allergy. Please indicate how much of an impact each scenario has on your adolescent's quality of life by placing a tick or a cross in one of the boxes number 0-6. If you believe the scenario has no impact please choose 0 (not at all).

0	1	2	3	4	5	6
Not at all	Barely	Slightly	Moderately	Quite a bit	Very much	Extremely

Question	0	1	2	3	4	5	6
1. My teenager always eats the same foods because of food allergy.	☐	☐	☐	☐	☐	☐	☐
2. My teenager has a restricted diet because of food allergy.	☐	☐	☐	☐	☐	☐	☐
3. My teenager cannot experiment with different foods on holiday because of food allergy.	☐	☐	☐	☐	☐	☐	☐
4. My teenager misses out because of food allergy.	☐	☐	☐	☐	☐	☐	☐
5. My teenager is more cautious generally because of food allergy.	☐	☐	☐	☐	☐	☐	☐
6. My teenager sticks to foods he/she knows.	☐	☐	☐	☐	☐	☐	☐
7. My teenager has to be more sensible than his/her peers because of food allergy.	☐	☐	☐	☐	☐	☐	☐
8. My teenager takes more of an interest in food because of food allergy.	☐	☐	☐	☐	☐	☐	☐
9. My teenager reads the label on everything he/she eats.	☐	☐	☐	☐	☐	☐	☐
10. My teenager is frustrated about food labeling.	☐	☐	☐	☐	☐	☐	☐
11. My teenager is more wary of situations because of food allergy.	☐	☐	☐	☐	☐	☐	☐
12. My teenager feels different because he/she cannot eat what his/her friends can eat.	☐	☐	☐	☐	☐	☐	☐
13. My teenager feels anxious in restaurant.	☐	☐	☐	☐	☐	☐	☐
14. My teenager finds it difficult to ask about food ingredients in restaurant.	☐	☐	☐	☐	☐	☐	☐
15. My teenager avoids telling people about his/her food allergy until he/she knows them well.	☐	☐	☐	☐	☐	☐	☐
16. My teenager gets irritated by his/her food allergy.	☐	☐	☐	☐	☐	☐	☐
17. My teenager worries as he/she always has to carry a bag because of his/her medication.	☐	☐	☐	☐	☐	☐	☐
18. School trips away are not easy for my teenager.	☐	☐	☐	☐	☐	☐	☐
19. My teenager worries that he/she can only eat in a limited range of restaurants.	☐	☐	☐	☐	☐	☐	☐
20. My teenager has been really scared by having a reaction.	☐	☐	☐	☐	☐	☐	☐
21. My teenager feels nervous around the food they are allergic to because of food allergy.	☐	☐	☐	☐	☐	☐	☐
22. My teenager gets frightened about food allergy.	☐	☐	☐	☐	☐	☐	☐
23. I feel my teenager has had to grow up more quickly because of food Allergy.	☐	☐	☐	☐	☐	☐	☐
24. My teenager has to be more responsible than other teenagers.	☐	☐	☐	☐	☐	☐	☐
25. My teenager has been teased because of food allergy.	☐	☐	☐	☐	☐	☐	☐
26. My teenager gets frustrated because of food allergy.	☐	☐	☐	☐	☐	☐	☐
27. My teenager feels different to other teenagers because of food allergy.	☐	☐	☐	☐	☐	☐	☐



Chapter 7

Food allergy-related quality of life after double-blind placebo-controlled food challenges in adults, adolescents and children

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ABSTRACT

Objective: Currently, the longitudinal validity (validity over time) and responsiveness (ability to measure change over time) of the Food Allergy Quality of Life Questionnaire-Adult Form, -Teenager Form and -Child Form (FAQLQ-AF, -TF, -CF) are unknown. Additionally, the self-reported impact of a double-blind placebo-controlled food challenge (DBPCFC) on health-related quality of life (HRQL) in adults (≥18 years), adolescents (13-17 years) and children (8-12 years) is currently unknown. The aims of this study were to assess the longitudinal validity and responsiveness of the FAQLQ-AF, -TF and -CF and to assess the impact of a DBPCFC on HRQL.

Methods: Two-hundred-and-twenty-one participants suspected of food allergy were included from Dutch allergy centers. Participants undergoing a DBPCFC (experimental group) completed the FAQLQ and Food Allergy Independent Measure (FAIM) 1 month before (baseline) and 6 months after (follow-up) a DBPCFC. Participants not undergoing a DBPCFC (control group) completed the questionnaire-package twice with a seven-month interval.

Results: HRQL improved following a DBPCFC with greater improvements in HRQL following a negative outcome (food allergy ruled out) than a positive outcome (food allergy confirmed), demonstrating responsiveness of the FAQLQs. Significant correlations were shown between the change (follow-up minus baseline) in FAQLQ and FAIM scores supporting the longitudinal validity of these questionnaires: FAQLQ-AF (Pearson=0.71, $p<0.001$), FAQLQ-TF (Pearson=0.35, $p=0.018$) and FAQLQ-CF (Pearson=0.51, $p<0.001$).

Conclusions: Our findings demonstrate the longitudinal validity and responsiveness of the FAQLQs. Greater improvements in HRQL were shown after a negative outcome than a positive outcome.

INTRODUCTION

Food is essential for life and important in social activities. Consequently, living with food allergy may seriously disrupt daily life of food allergic patients[1]. They are often afraid of allergic reactions on accidental exposure and are continuously faced with dietary and social restrictions[2]. Health-Related Quality of Life (HRQL) instruments can be used as outcome measures to evaluate this impact of food allergy and its subsequent interventions on HRQL[3]. HRQL is of particular interest as an outcome measure for food allergy, because symptoms of this disease are infrequent and mortality is low.

Recently, the self-administered Food Allergy Quality of Life Questionnaire-Adult Form, -Teenager Form and -Child Form (FAQLQ-AF, -TF, -CF) were developed for measuring HRQL in food allergic patients[2,4,5]. The FAQLQ-AF, -TF and -CF were shown to be valid, reliable and discriminative instruments[2,4-6]. However, HRQL-instruments that will be used as outcome measures in clinical trials must correlate over time with other relevant measures (longitudinally validity) and must be able to measure small but relevant HRQL changes over time (responsiveness)[3,7]. Currently, the longitudinal validity and responsiveness of the FAQLQ-AF, -TF and -CF are unknown.

A double-blind placebo-controlled food challenge (DBPCFC), which is the gold standard for diagnosing food allergy, is likely to cause HRQL changes over time, especially if the test is negative (food allergy ruled out). Until now, only one study has been published on the impact of food challenges on HRQL. This study showed that parent-proxy-reported HRQL of food allergic children (0-12 years) improves following a food challenge[3]. So far, no studies have been published on the impact of a DBPCFC on HRQL in adolescents (13-17 years) and adults (≥18 years). As these age-groups are developmentally different, the experience of food allergy and its subsequent interventions may differ for each age-group. Additionally, no studies have been published on the impact of a DBPCFC on HRQL in children (8-12 years) from the child's perspective, whereas it is well known that there generally is child-parent disagreement on the child's HRQL[8,9]. Finally, no studies have been published comparing HRQL in participants who undergo a DBPCFC with control participants.

Therefore, the aims of this study were to investigate the longitudinal validity and responsiveness of the FAQLQs and to investigate the self-reported impact of a DBPCFC on HRQL of food allergic adults, adolescents and children.

METHODS

Participants and procedures

Adults (≥18 years), adolescents (13-17 years) and children (8-12 years), who were awaiting a clinically indicated DBPCFC were included from Dutch allergy centers in Groningen and

Voorburg between May 2007 and January 2011. The only criterion used for referral for DBPCFC was a clinical suspicion of food allergy. IgE measurements, skin prick tests or prior history of anaphylaxis were not routinely used in our decision to refer for DBPCFC. The two centers collaborate on uniform methodology of DBPCFC procedure[10,11]. A DBPCFC consists of a placebo and active challenge, which were randomly administered on separate days with at least a two-week interval in between. Participants and any individuals with patient contact were blinded to the sequence of the two challenges.

All patients visiting the clinic with suspected food allergy were placed on the waiting list for a DBPCFC on a first come first served basis. Participants were included in the experimental group or control group based on the expected duration of time spent on the waiting list for DBPCFC. Participants who were expected to have a DBPCFC within six months were included in the experimental group and completed the questionnaire-package at home one month before (baseline) and six months after (follow-up) a DBPCFC (placebo and active challenge) was performed. Participants who were not expected to have a DBPCFC within six months were included in the control group and completed the questionnaire-package twice with a seven-month interval without undergoing a DBPCFC (no placebo or active challenge). Additionally, participants recruited through Dutch food allergy support organizations were included in the control group when they reported a physician diagnosed food allergy.

Participants were excluded from the study if diagnostic/therapeutic interventions or accidental ingestions resulting in clinical allergic reactions (Mueller classification grade III/IV) had taken place between baseline and follow-up measurement or when less than 85% of the questions were completed. Possible differences between descriptive characteristics of participants recruited in the participating centers and between participants from the control and experimental group were examined using Chi-square-test (nominal data) and Mann-Whitney-test (ordinal, continuous data).

This study was approved by the local medical ethics review commission who deemed that permission from the commission was not required.

Questionnaires

Food Allergy Quality of Life Questionnaires (FAQLQs)

The Dutch FAQLQ-Adult Form (FAQLQ-AF)[2], -Teenager Form (FAQLQ-TF)[5] and -Child Form (FAQLQ-CF)[4] are self-reported, disease-specific instruments for measuring the impact of food allergy on the adult's (≥18 years)[2], adolescent's (13-17 years)[5] and child's (8-12 years) HRQL[4], respectively. The FAQLQ-AF contains 29 items and 4 domains (Risk of Accidental Exposure, Emotional Impact, Allergen Avoidance & Dietary Restrictions, and Food Allergy related Health). The FAQLQ-TF contains 23 items and 3 domains (Allergen Avoidance & Dietary Restrictions, Risk of Accidental Exposure, and Emotional impact). The FAQLQ-CF contains 24 items and 4 domains (Risk of Accidental Exposure, Emotional Impact, Allergen

Avoidance, and Dietary Restrictions). Each item is scored on a seven-point scale. Total FAQLQ score of each questionnaire is the mean of all items and ranges from 1 (minimal impairment in HRQL) to 7 (maximal impairment in HRQL).

Food Allergy Independent Measure (FAIM)

The FAIM[12], a self-report instrument, reflects the participant's perceived food allergy severity and food allergy-related risk. The FAIM consists of four expectation of outcome questions, which capture the participants' perceived expectation of the chance of accidental exposure and of what will happen following accidental exposure. These expectations are likely to be the source/predictors of HRQL changes in anaphylactic disorders[13]. Additionally, the FAIM contains two questions which reflect disease severity. Each question was scored on a seven-point scale. Total FAIM score is the mean of all items and ranges from 1 (limited severity perception) to 7 (greatest severity perception). Instruments based on the method of expectation of outcome questions have proved to be useful independent measures for evaluating the construct validity of HRQL-instruments[2,4,5,14-16] and are used in this study to evaluate the longitudinal validity of the FAQLQs.

Statistical analysis

Data were analyzed using SPSS software for Windows (Version 18.0).

Change in HRQL and perceived disease severity following DBPCFC

Changes in HRQL (follow-up minus baseline FAQLQ scores) were tested for significance (Wilcoxon signed rank test). P values ≤0.05 were considered to be statistically significant. The overall difference in HRQL changes was calculated as follows: HRQL change experimental group minus HRQL change control group. Following the outcome of the DBPCFC, participants in the experimental group (Exp_total) were split into three groups: 1. positive outcome, i.e. food allergy in question confirmed (Exp_pos), 2. negative outcome, i.e. food allergy in question ruled out (Exp_neg), 3. questionable outcome, i.e. food allergy not confirmed/not ruled out (Exp_quest). Additionally, a subgroup analysis was performed on participants with a negative outcome and no remaining other food allergy (Exp_neg_NRFA). Changes in FAIM scores were analyzed in the same way.

Relevance of changes in HRQL following DBPCFC

Both a statistical and clinical method were used to evaluate whether a change in HRQL was considered to be relevant.

Firstly, the smallest change in HRQL that is considered to be statistically important is called the standard error of measurement ($SEM = \sigma_x\sqrt{1-r_{xx}}$) [17,18]. σ_x represents the standard deviation of the FAQLQ baseline measurement and r_{xx} represents the reliability or intra class correlation coefficient of the FAQLQs[6,14].

Secondly, the smallest change in HRQL that is considered to be clinically important by participants, is called the minimal important difference (MID)[19]. The MID has been estimated to be approximately 0.5 in several HRQL questionnaires using a seven-point scale[3,17,19,20] and can be used to calculate the therapeutic value of an intervention. The therapeutic value of an intervention is defined as the number of participants who need to undergo the intervention for one participant to have a clinically important improvement over and above that which he/she would have experienced with the control intervention. The therapeutic value of a DBPCFC was calculated using the methodology of numbers needed to treat (NNT)[21]. Percentages of participants who improve, remain stable and deteriorate were calculated as follows: change in HRQL scores <-0.5 (important improvement in HRQL), between -0.5 and 0.5 (unchanged HRQL) and >0.5 (important deterioration in HRQL). The proportion of participants who fared better following a DBPCFC or who fared better in the control group were calculated from the proportion of participants with an important improvement in HRQL, unchanged HRQL or an important deterioration in HRQL (table 1). The overall proportion of participants who benefit from a DBPCFC is the difference of the two abovementioned proportions. The NNT of a DBPCFC is the reciprocal of the proportion of participants benefiting from DBPCFC.

Table 1. Calculation of the proportion of patients showing improvement (HRQL change<-0.5), no change (HRQL change between -0.5&0.5) or deterioration (HRQL change>0.5) in their HRQL following a Double Blind Placebo Controlled Food Challenge (DBPCFC)

		Negative outcome DBPCFC (food allergy ruled out)			**Positive outcome DBPCFC (food allergy confirmed)**		
	Proportions DBPCFC	**improved (u)**	**unchanged (v)**	**deteriorated (w)**	**improved (x)**	**Unchanged (y)**	**deteriorated (z)**
	Adults	(0.63)	(0.25)	(0.13)	(0.46)	(0.42)	(0.13)
Proportions	Adolescents	(0.69)	(0.23)	(0.08)	(0.28)	(0.48)	(0.24)
Control group	Children	(0.39)	(0.48)	(0.13)	(0.42)	(0.45)	(0.13)
improved	**(a)**	**(au)**	**(av)**	**(aw)**	**(ax)**	**(ay)**	**(az)**
Adults	(0.25)	0.16	0.06	0.03	0.11	0.10	0.03
Adolescents	(0.44)	0.30	0.10	0.03	0.12	0.21	0.11
Children	(0.20)	0.08	0.10	0.03	0.08	0.09	0.03
unchanged	**(b)**	**(bu)**	**(bv)**	**(bw)**	**(bx)**	**(by)**	**(bz)**
Adults	(0.75)	0.47	0.19	0.09	0.34	0.31	0.09
Adolescents	(0.48)	0.33	0.11	0.04	0.13	0.23	0.12
Children	(0.55)	0.22	0.26	0.07	0.23	0.25	0.07
deteriorated	**(c)**	**(cu)**	**(cv)**	**(cw)**	**(cx)**	**(cy)**	**(cz)**
Adults	(0.00)	0.00	0.00	0.00	0.00	0.00	0.00
Adolescents	(0.08)	0.06	0.02	0.01	0.02	0.04	0.02
Children	(0.25)	0.10	0.12	0.03	0.10	0.11	0.03

The proportion of patients who fared better following a negative DBPCFC is the sum of **bu, cu** and **cv**. The proportion of patients who fared better in the control group is the sum of **av, aw** and **bw.**
The proportion of patients whose outcome is the same irrespective of a positive diagnosis is the sum of **au, bv** and **cw**. Proportions following a positive DBPCFC were calculated in the same way.

Factors influencing HRQL changes

Multiple linear regression analysis was performed to correct for factors possibly influencing change in HRQL. The change in FAQLQ scores was used as the dependent variable. The outcome of the DBPCFC (positive versus control/ negative versus control) and possible confounders (type of recruitment, center of recruitment, age, baseline HRQL scores and number of food allergies) were used as independent variables.

Responsiveness of the FAQLQs

Changes in HRQL scores were calculated and tested for significance (see change in HRQL following DBPCFC) to investigate the ability of the FAQLQs to measure relevant changes over time (responsiveness),

Longitudinal validity of the FAQLQs

Pearson's correlation coefficients were calculated between the change in FAQLQ scores and change in FAIM scores to assess the longitudinal validity of the FAQLQs. Moderate correlations were expected[22].

RESULTS

Participants

Questionnaire packages were sent to 392 participants and returned by 299 participants (response rate 76%) (Table 2). Follow-up questionnaire packages were returned by 235 participants (response rate 79%). Fourteen participants were excluded (reasons listed in table 2). Therefore, 221 participants were eligible for analysis. Participant characteristics are shown in Table 3. There were no significant differences between participants in the control group and the experimental group, except for the mean age of adults (control group 49.3 years, experimental group 32.4 years, p=0.002). Specifically, there were no differences between participants recruited from the two participating centers (experimental group) or between participants recruited by advertisement or from the clinic (control group) [data not shown].

Change in HRQL following DBPCFC

There were no significant differences in baseline HRQL (FAQLQ) scores between the experimental and control group (adults p=0.956, adolescents p=0.622 and children p=0.908) or between patients recruited from the two participating centers (adolescents p=0.782, children p=0.384) or between participants recruited by advertisement or from the clinic (adolescents p=0.777) except for adults (5.68 vs 3.78, p=0.009).

Table 2. Flow chart participant recruitment

	All ages	≥18 years	13-17 years	8-12 years
Recruited participants, n	392	137	117	138
Returned 1st packages, n	299	92	96	111
Returned 2nd packages, n	235	79	77	79
Excluded participants, n	14	6	6	2
<85% of questions completed	4	1	1	2
Management intervention	6	2	4	-
Did not complete DBPCFC	3	3	-	-
Severe anaphylactic reaction prior to follow up measurement	1	-	1	-
Included, n	221	73	71	77
Experimental (Voorburg/Groningen), n	156 (20/136)	53 (0/53)	46 (6/40)	57 (14/43)
Control, n (clinic/food allergy support organizations)	65 (42/23)	20 (14/6)	25 (9/16)	20 (19/1)

Table 3. Participant characteristics

Age-group	**≥18 years**			**13-17 years**			**8-12 years**		
	n[1]	**%**[2]	**(n, exp**[3]**)**	**n**	**%**	**(n, exp)**	**n**	**%**	**(n, exp)**
Number	**73**	100%	(53)	**71**	100%	(46)	**77**	100%	(57)
Sex, female	**58**	79%	(44)	**35**	49%	(23)	**29**	38%	(22)
male	**15**	21%	(9)	**36**	51%	(23)	**48**	62%	(35)
Mean age, years (SD)	**35.8**		(14.9)	**15.2**		(1.4)	**10.4**		(1.6)
DBPCFC									
Peanut	**20**	27%	(20[4])	**23**	32%	(23)	**25**	32%	(25)
Nut	**12**	16%	(12)	**9**	13%	(9)	**18**	23%	(18)
Milk	**2**	3%	(2)	**8**	11%	(8)	**7**	9%	(7)
Egg	**3**	4%	(3)	**3**	4%	(3)	**5**	6%	(5)
Wheat	**8**	11%	(8)	-			**1**	1%	(1)
Soy	**4**	5%	(4)	**3**	4%	(3)	**1**	1%	(1)
Sesame	**4**	5%	(4)	-			-		
Number of food allergies									
1 food	**17**	23%	(13)	**12**	17%	(9)	**20**	26%	(13)
2 foods	**14**	19%	(12)	**22**	31%	(13)	**26**	34%	(17)
3 foods	**12**	16%	(9)	**15**	21%	(9)	**12**	16%	(10)
> 3 foods	**30**	41%	(19)	**22**	31%	(15)	**19**	25%	(17)
Symptoms									
Cardiovascular	**39**	53%	(29)	**34**	48%	(21)	**19**	25%	(13)
Respiratory	**67**	92%	(49)	**61**	86%	(42)	**58**	75%	(41)
Gastro-intestinal	**44**	60%	(31)	**43**	61%	(28)	**41**	53%	(26)
Skin	**53**	73%	(38)	**50**	70%	(30)	**46**	60%	(32)
Ever experienced anaphylaxis?									
Yes	**62**	85%	(46)	**55**	77%	(35)	**56**	73%	(41)
No	**11**	15%	(7)	**16**	23%	(11)	**21**	27%	(16)

1 n = number of participants (sum of experimental and control)
2 % = percentage of participants (sum of experimental and control)
3 (exp) = the number of participants in the experimental group
4 DBPCFC not performed in participants of the control group

For adults, HRQL improved significantly following a DBPCFC when all outcomes of the test were combined (baseline=4.35, follow-up=3.81, p=0.001, n=53), whereas HRQL of participants in the control group did not change significantly (baseline=4.35, follow-up=4.24, p=0.421, n=20) (Table 4).

Table 4. Mean Food Allergy Quality of Life (FAQLQ) scores and Food Allergy Independent Measure (FAIM) scores following DBPCFC

	FAQLQ scores			FAIM scores		
Age (years) **Number (exp/con)** **Outcome DBPCFC**	**≥18 (53/20)**	**13-17 (46/25)**	**8-12 (57/20)**	**≥18 (53/20)**	**13-17 (46/25)**	**8-12 (57/20)**
Exp_Total[1], n	53	46	57	53	46	57
Baseline (SD)	4.35 (1.15)	3.89 (1.03)	3.80 (1.45)	3.84 (0.92)	3.48 (0.86)	3.35 (0.97)
Follow-up (SD)	3.81 (1.35)	3.65 (1.32)	3.25 (1.39)	3.31 (1.01)	3.33 (1.05)	3.19 (1.02)
P value	**0.001**	0.169	**0.002**	**0.001**	0.264	0.292
Exp_Pos[2], n	24	29	31	24	29	31
Baseline (SD)	4.56 (0.93)	3.93 (1.12)	3.75 (1.44)	3.91 (0.78)	3.66 (0.89)	3.35 (0.97)
Follow-up (SD)	4.21 (1.21)	3.92 (1.15)	3.36 (1.28)	3.71 (0.92)	3.76 (0.88)	3.33 (0.89)
P value	**0.036**	0.905	**0.041**	0.295	0.535	0.857
Exp_Neg[3], n	24	13	23	24	13	23
Baseline (SD)	4.24 (1.36)	3.68 (0.90)	3.93 (1.47)	3.89 (1.08)	3.10 (0.83)	3.38 (0.96)
Follow-up (SD)	3.36 (1.47)	2.71 (1.29)	3.14 (1.54)	2.91 (1.03)	2.35 (0.90)	3.02 (1.21)
P value	**0.009**	**0.013**	**0.018**	**<0.001**	**0.013**	0.153
Exp_Neg_NRFA[3a], n	6	4	4	6	4	4
Baseline (SD)	4.20 (1.85)	3.71 (0.75)	3.39 (1.51)	4.17 (1.42)	2.75 (0.67)	3.54 (1.09)
Follow-up (SD)	1.97 (1.41)	1.58 (0.50)	2.55 (1.51)	2.00 (0.62)	1.33 (0.24)	2.88 (1.71)
P value	**0.046**	0.068	0.465	**0.042**	0.068	0.380
Exp_Quest[4], n	5	4	3	5	4	3
Baseline (SD)	3.93 (1.01)	4.32 (0.69)	3.21 (1.70)	3.30 (0.70)	3.42(0.29)	3.11 (0.59)
Follow-up (SD)	4.16 (0.77)	4.72 (1.02)	2.97 (1.62)	3.31 (0.67)	3.35 (0.36)	3.11 (0.59)
P value	0.225	0.273	0.593	1	0.593	1
Control group n	20	25	20	20	25	20
Baseline (SD)	4.35 (1.52)	4.03 (1.28)	3.77 (1.27)	3.79 (1.14)	3.75(1.07)	3.31 (0.98)
Follow-up (SD)	4.24 (1.53)	3.69 (1.19)	3.84 (1.20)	3.67 (1.18)	3.79 (0.85)	3.37 (1.01)
P value	0.421	**0.018**	0.763	0.195	0.884	0.751

[1] Exp_total: Experimental group (exp)
[2] Exp_pos: Experimental group, positive outcome of the DBPCFC
[3] Exp_neg: Experimental group, negative outcome of the DBPCFC
[3a] Exp_negative_NRFA Experimental group, negative outcome of the DBPCFC and no remaining food allergy
[4] Exp_quest: Experimental group, questionable outcome of the DBPCFC

A great improvement in HRQL was shown following a negative outcome (food allergy ruled out, n=24) and when there was no remaining other food allergy (baseline=4.20, follow-up=1.97, p=0.046, n=6). A smaller significant improvement in HRQL was shown following a positive outcome (baseline=4.56, follow-up=4.21, p=0.036, n=24). Following a questionable outcome, there was no significant change in HRQL (baseline=3.93, follow-up=4.16, p=0.225, n=5). For children, similar results were shown. For adolescents, HRQL improved significantly following a negative DBPCFC (baseline=3.68, follow-up=2.71, p=0.013, n=13). However, HRQL did not improve significantly following a positive outcome (baseline=3.93, follow-up=3.92, p=0.905, n=29), whereas the HRQL of participants in the control group improved significantly (baseline=4.03, follow-up=3.69, p=0.018, n=25).

Relevance of changes in HRQL following DBPCFC

In order to assess the relevance of HRQL changes from a statistical and clinical point of view, the Standard error of measurement (SEM) was calculated (FAQLQ-AF=0.25, FAQLQ-TF=0.16, and FAQLQ-CF=0.44) and the minimal important difference (MID) of 0.5 was used. The MID is the smallest difference in HRQL that is considered to be clinically important by patients. The overall improvement in HRQL following a negative DBPCFC exceeded the SEM and MID for adults, adolescents and children and was therefore considered to be statistically and clinically relevant (table 5). The overall differences in HRQL following a positive outcome of a DBPCFC only reached the SEM and were therefore considered to be statistically relevant. The overall improvement in HRQL nearly reached the MID for children.

Table 5. Number needed to treat (NNT) of a double-blind placebo-controlled food challenge (DBPCFC)

Outcome DBPCFC	Overall Difference HRQL[1]	Proportion better on DBPCFC[2]	Proportion better in control[2]	Proportion benefiting DBPCFC[3]	NNT
Negative					
Adults	-0.76 **(p=0.023)**	0.47	0.19	0.28	3.56
Adolescents	-0.62 **(p=0.040)**	0.41	0.17	0.23	4.28
Children	-0.87 **(p=0.023)**	0.43	0.19	0.24	4.18
Positive					
Adults	-0.24 (p=0.240)	0.34	0.23	0.11	8.75
Adolescents	0.34 (p=0.078)	0.19	0.43	-0.24	-4.15
Children	-0.47 (p=0.065)	0.45	0.19	0.26	3.83

1 Overall difference Health-related Quality of Life (HRQL) = change experimental group (follow-up minus baseline HRQL scores) minus change control group. A negative overall difference represents an improvement in HRQL.

2 Proportion better on DBPCFC or proportion better in control group were calculated from the proportion of participants with an important improvement in HRQL, unchanged HRQL or an important deterioration in HRQL (**table 1**).

3 Proportion benefiting DBPCFC is the difference of the two abovementioned proportions.

The proportion of participants with a clinically important improvement in HRQL (<-0.5) following a negative outcome of a DBPCFC was higher than in the control group (figure 1, Table 1). The proportions of participants whose HRQL was the same (-0.5 to 0.5) following a negative outcome was lower than in the control group. The proportion of participants with an important deterioration in HRQL (>0.5) were 13% (adults), 8% (adolescents) and 13% (children) following a negative DBPCFC compared to 25% (adults), 8% (adolescents) and 0% (children) in the control group. The NNT of a negative DBPCFC was 4 (table 5). Thus, for every 4 participants who have a negative DBPCFC 1 participant has a clinically important improvement in HRQL.

Following a positive DBPCFC, the NNT was higher (indicating lower effectiveness) compared to adults with a negative DBPCFC (table 5). Remarkably, adolescents in the control group fared better than adolescents following a positive DBPCFC (table 5, Figure 1).

Factors influencing HRQL changes

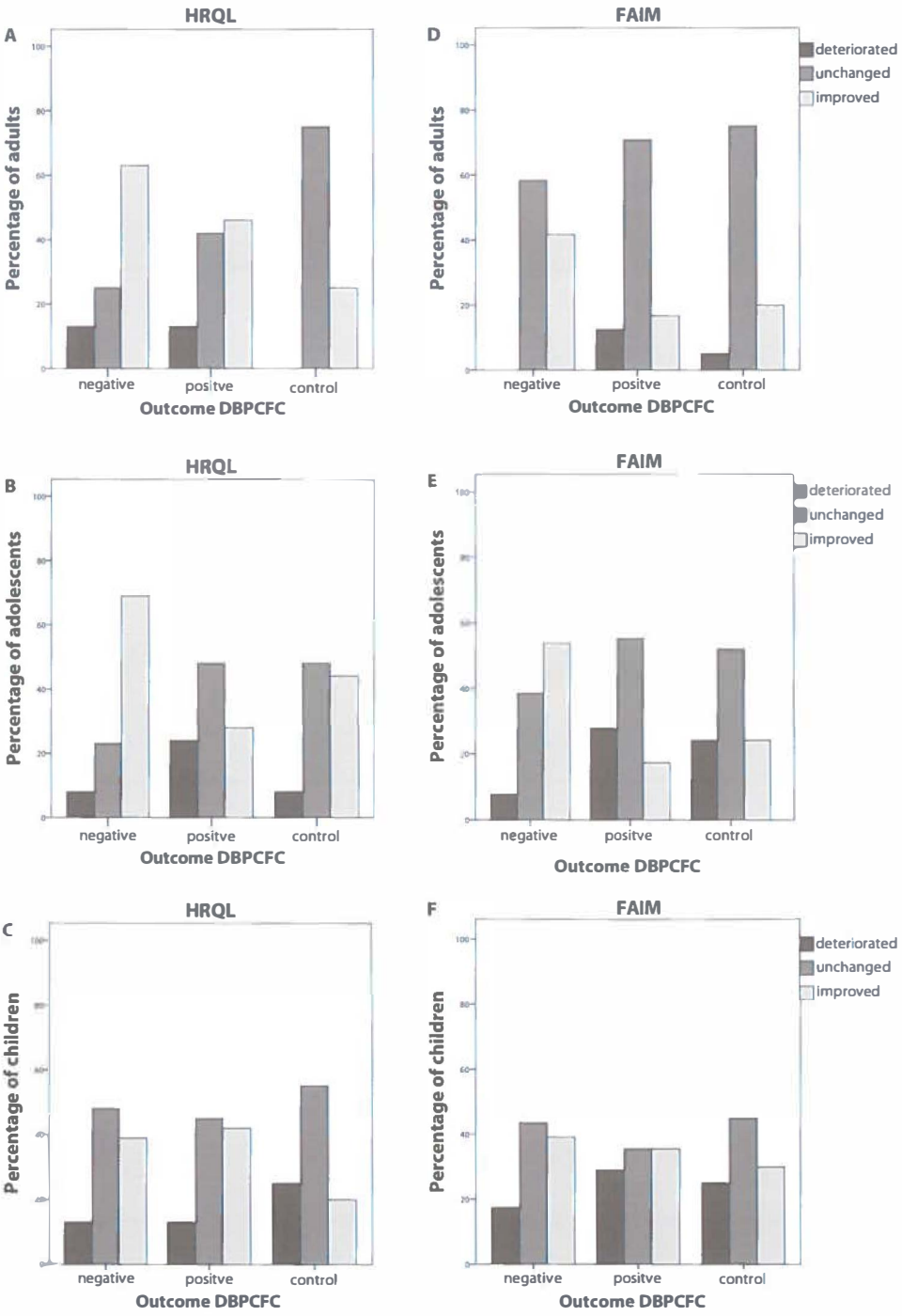
A negative outcome of the DBPCFC resulted in improvement of HRQL compared to the control group after correction for confounding (Table 6). A positive outcome of the DBPCFC resulted in improvement of HRQL after correction for confounding in children. Having more than two food allergies was associated with deterioration in HRQL for children. Higher FAQLQ baseline scores (poorer HRQL) contributed significantly to improvement in HRQL for all ages.

Table 6. Factors influencing change in HRQL scores (follow-up minus baseline) following positive and negative DBPCFC using multiple linear regression analysis

	Adults				Adolescents				Children			
	B[1]	P	95%	CI	B	P	95%	CI	B	P	95%	CI
Outcome test												
Positive (control vs positive)	-0.16	0.68	-0.91	0.59	0.34	0.43	-0.52	1.20	-0.94	0.02	-1.74	-0.18
Negative (control vs negative)	-0.74	0.03	-1.42	-0.06	-0.70	0.011	-1.56	0.17	-1.19	0.00	-1.94	-0.45
Age (years)	-0.01	0.42	-0.03	0.01	-0.08	0.23	-0.22	0.05	0.06	0.42	-0.09	0.21
Number of food allergies (≤2 vs >2)	0.39	0.14	-0.13	0.92	0.31	0.16	-0.13	0.74	0.50	0.04	0.02	0.99
FAQLQ baseline (1=best HRQL to 7= worst HRQL)	-0.26	0.02	-0.47	-0.05	-0.27	0.01	-0.45	-0.08	-0.37	0.00	-0.55	-0.20
Center recruitment (Voorburg vs Groningen)	n.a.	n.a.	n.a.	n.a.	-0.44	0.24	-1.17	0.30	0.38	0.24	-0.26	1.01
Type of recruitment (clinic vs advertisement)	-0.21	0.71	-0.89	1.31	-0.52	0.11	-1.16	0.12	n.a.	n.a.	n.a.	n.a.

1 A negative B coefficient represents an improvement in HRQL. P values ≤0.05 were considered to be statistically significant.

Figure 1. Percentages of participants whose HRQL deteriorate (change>0.5), show no change (change between -0.5&0.5) or improve (change<-0.5 following a double-blind placebo-controlled food challenge in A) Adults, B) Adolescents and C) Children. Additionally, Percentages of participants whose FAIM deteriorate, show no change or improve in D) Adults, E) Adolescents, and F) Children.



Change in perceived disease severity (FAIM) following DBPCFC

There were no significant differences in baseline FAIM scores between participants in the control and experimental group (adults: p=0.701, adolescents p=0.199, children p=0.986) or between participants recruited from the two participating centers (adolescents p=0.410, children p=0.875) or between participants recruited by advertisement or from the clinic (adults p=0.148, adolescents p=0.393).

For adults, FAIM scores improved significantly following a DBPCFC when all outcomes of the test were combined (baseline=3.84, follow-up=3.31, p=0.001) (Table 4). A great improvement in perceived disease severity was shown following a negative outcome (baseline=3.89, follow-up=2.91, p<0.001). No improvement in perceived disease severity was shown following a positive outcome (baseline 3.91, follow-up=3.71, p=0.295). No change in perceived disease severity was shown in the control group (baseline=3.79, follow-up=3.67, p=0.195). Similar results were shown for adolescents and children. The percentages of participants with a clinically important change in FAIM score are shown in figure 1.

Responsiveness

All FAQLQs were able to measure changes exceeding the SEM and MID of the FAQLQs (Table 4). This supports the responsiveness of all FAQLQs.

Longitudinal validation

Significant correlations were shown between the change in FAQLQ scores and the change in FAIM scores for the FAQLQ-AF (Pearson 0.71, p<0.001), FAQLQ-TF (Pearson=0.35, p=0.018) and FAQLQ-CF (Pearson=0.51, p<0.001). This supports the longitudinal validity of the FAQLQs.

DISCUSSION

This study examined for the first time the longitudinal validity and responsiveness of the FAQLQ-AF, -TF and -CF and the self-reported impact of a DBPCFC on HRQL of food allergic patients. All FAQLQs were able to measure relevant changes in HRQL and correlated significantly to measures of perceived disease severity. These findings thus support the responsiveness and longitudinal validity of the FAQLQ-AF, -TF and -CF and the suitability of these instruments as outcome measures. Additionally, this study shows that adults, adolescents and children benefit from a negative DBPCFC and children even benefit if the outcome is positive. The NNT of a negative DBPCFC was four. Thus, for every four participants who have a negative DBPCFC, one participant has a clinically important improvement in HRQL. These findings thus support the large impact of food allergy on HRQL and illustrate which patients benefit from DBPCFC.

Overall, our findings are in agreement with previous literature, which showed that parent-proxy-reports on the child's HRQL improved significantly following a food challenge in children aged 0-12 years and that larger improvements in HRQL were shown following a negative outcome than following a positive outcome[3]. Additionally, other studies on parents' perceptions of their child's food challenge[23-26] showed reduced parental concerns[25,26] and parental anxiety[24] following food challenges irrespective of the outcome of the challenge. It was hypothesized that these improvements in HRQL/wellbeing were caused by the fact that a definitive diagnosis provides a sense of certainty. This hypothesis was based on findings that the main concerns of food allergic patients and their families were uncertainty and lack of information rather than fear of the challenge procedure[3] and that a greater certainty of the diagnosis following a positive or negative outcome was perceived as positive in egg allergic children[26]. This hypothesis is further supported by our data showing no improvement in HRQL following challenges with an uncertain outcome. Thus, by providing a sense of certainty, a food challenge may have a positive impact on HRQL, irrespective of the outcome[3,26] .

There is much discussion on the interpretation of HRQL changes[19,27-32]. Different methods can be used to determine a minimal important change (the change in HRQL that is considered clinically relevant). Such methods may be distribution-based or anchor-based. Distribution-based methods, such as the SEM, rely on scoring methods of an instrument and the distribution of the results[29]. Anchor-based methods use an external criterion (anchor) to interpret whether a particular magnitude of change is meaningful for patients/clinicians. As it is necessary to know whether the observed change is important from the patient's/clinician's perspective, anchor-based methods are still preferred in assessing the MID[19]. In our study, a distribution-based method (SEM) as well as an anchor-based method (MID) were used. We found a statistically and clinically relevant change in HRQL following a negative DBPCFC, and for children following a positive DBPCFC.

Although HRQL of adolescents improves significantly following a negative DBPCFC, some remarkable findings were shown for adolescents. Firstly, adolescents' HRQL did not improve following a positive outcome. Several factors may explain this finding. As different issues relating to food allergy may have different impacts at different stages of life[2,4,5], the experience of food allergy-related interventions, such as DBPCFC, may differ for each age-group as well. It may be that the impact of the feeling of certainty of diagnosis following a DBPCFC on HRQL, as is suggested by studies of parents of food allergic children[23-26], is less relevant for adolescents themselves, because it is overshadowed by the impact of peer comparison and peer pressure[3,33,34] on adolescent's perception of living with food allergy. A second remarkable finding was that HRQL of adolescents in the control group improved significantly, although less than the MID of 0.5 Despite this, the overall improvement in HRQL following a negative DBPCFC (improvement experimental group minus improvement control group) was statistically and clinically significant 0.62

(p=0.040). However, the nature of factors associated with HRQL changes in adolescents requires further investigation, because no predictive factors were identified in this study.

Another unexpected finding was that HRQL of some participants deteriorated following a negative DBPCFC, even though this only occurred in seven participants. Further characterization of these participants showed that some participant characteristics tended to be more common in participants whose HRQL deteriorated following a negative DBPCFC compared to participants whose HRQL did not deteriorate. These factors are number of food allergies (4/2, p=0.062), percentage of peanut challenges (57%/21%, p=0.079) and percentage of participants who did not eat the tested food despite the negative DBPCFC (57%/33%, p=0.108). We hypothesize that these factors may influence deterioration in HRQL following a negative challenge. However, this needs further investigation with larger numbers of patients.

This study also has some limitations. Although there was sufficient power to determine the longitudinal validity and responsiveness of the FAQLQ-AF, -TF and -CF and to determine the overall impact of a DBPCFC on HRQL, the power to study the impact of a DBPCFC in the different subgroups (age-specific & DBPCFC-outcome-specific) is moderate. Therefore, the sub-group analyses should be interpreted with caution. Secondly, the majority of participants was peanut or nut allergic, which may limit the generalisability of these findings to patients with other food allergies. Thirdly, due to logistic and ethical reasons we assigned participants to the control and experimental group based on the expected duration of time spent on the waiting list. Therefore, we corrected for possible confounders, such as method of recruitment, age and baseline HRQL scores. While a true randomized trial still is methodologically preferred it may be difficult to generalize results obtained from participants willing to be randomized to postponement of a DBPCFC to most other food allergic individuals.

In summary, our results support the longitudinal validity and responsiveness of the FAQLQ-AF, -TF and -CF and the suitability of these instruments as outcome measures. Additionally, a DBPCFC is considered to be a time-consuming process and has previously been discussed in the literature as being potentially burdensome to patients. However, our study shows that children, adolescents and adults benefit from a negative DBPCFC and its subsequent changes in management, and children do so even if the outcome is positive. Thus, a DBPCFC is not only the gold standard for diagnosing food allergy, but also improves patient HRQL for specified groups. This provides clinicians with an additional reason to promote the use of DBPCFCs. Information from self-reported FAQLQs will help to optimize such interventions from a HRQL point of view. Further research is needed to study the predictors of HRQL changes following DBPCFC.

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REFERENCE LIST

1. Flokstra-de Blok BM, Dubois AE, Vlieg-Boerstra BJ, et al. Health-related quality of life of food allergic patients: Comparison with the general population and other diseases. Allergy 2010; 65:238-44.
2. Flokstra-de Blok BM, van der Meulen GN, DunnGalvin A, et al. Development and validation of the food allergy quality of life questionnaire - adult form. Allergy 2009; 64:1209-17.
3. DunnGalvin A, Cullinane C, Daly DA, Flokstra-de Blok BM, Dubois AE, Hourihane JO. Longitudinal validity and responsiveness of the food allergy quality of life questionnaire - parent form in children 0-12 years following positive and negative food challenges. Clin Exp Allergy 2010; 40:476-85.
4. Flokstra-de Blok BM, DunnGalvin A, Vlieg-Boerstra BJ, et al. Development and validation of a self-administered food allergy quality of life questionnaire for children. Clin Exp Allergy 2009; 39:127-37.
5. Flokstra-de Blok BM, DunnGalvin A, Vlieg-Boerstra BJ, et al. Development and validation of the self-administered food allergy quality of life questionnaire for adolescents. J Allergy Clin Immunol. 2008; 122:139,44, 144.e1-2.
6. van der Velde JL, Flokstra-de Blok BM, Vlieg-Boerstra BJ, et al. Test-retest reliability of the food allergy quality of life questionnaires (FAQLQ) for children, adolescents and adults. Qual Life Res 2009; 18:245-51.
7. Oude Elberink JN, De Monchy JG, Van Der Heide S, Guyatt GH, Dubois AE. Venom immunotherapy improves health-related quality of life in patients allergic to yellow jacket venom. J Allergy Clin Immunol 2002; 110:174-82.
8. van der Velde JL, Flokstra-de Blok BM, Dunngalvin A, Hourihane JO, Duiverman EJ, Dubois AE. Parents report better health-related quality of life for their food-allergic children than children themselves. Clin Exp Allergy 2011; 41:1431-39.
9. van der Velde JL, Flokstra-de Blok BM, Hamp A, Knibb RC, Duiverman EJ, Dubois AE. Adolescent-parent disagreement on health-related quality of life of food-allergic adolescents: Who makes the difference? Allergy 2011; 66:1580-9.
10. Vlieg-Boerstra BJ, Herpertz I, Pasker L, et al. Validation of novel recipes for double-blind, placebo-controlled food challenges in children and adults. Allergy 2011; 66:948-54.
11. Vlieg-Boerstra B, Dubois A. Published recipes for double-blind placebo-controlled food challenges. Allergy 2005; 60:1212.
12. van der Velde JL, Flokstra-de Blok BM, Vlieg-Boerstra BJ, et al. Development, validity and reliability of the food allergy independent measure (FAIM). Allergy 2010; 65:630-5.
13. Oude Elberink JN. Significance and rationale of studies of health-related quality of life in anaphylactic disorders. Curr Opin Allergy Clin Immunol 2006; 6:298-302.
14. DunnGalvin A, de BlokFlokstra BM, Burks AW, Dubois AE, Hourihane JO. Food allergy QoL questionnaire for children aged 0-12 years: Content, construct, and cross-cultural validity. Clin Exp Allergy 2008; 38:977-86.
15. Cohen BL, Noone S, Munoz-Furlong A, Sicherer SH. Development of a questionnaire to measure quality of life in families with a child with food allergy. J Allergy Clin Immunol 2004; 114:1159-63.
16. Oude Elberink JN, de Monchy JG, Golden DB, Brouwer JL, Guyatt GH, Dubois AE. Development and validation of a health-related quality-of-life questionnaire in patients with yellow jacket allergy. J Allergy Clin Immunol 2002; 109:162-70.
17. Kocks JW, Tuinenga MG, Uil SM, van den Berg JW, Stahl E, van der Molen T. Health status measurement in COPD: The minimal clinically important difference of the clinical COPD questionnaire. Respir Res 2006; 7:62.
18. Norman GR, Sloan JA, Wyrwich KW. Interpretation of changes in health-related quality of life: The remarkable universality of half a standard deviation. Med Care 2003; 41:582-92.
19. Juniper EF, Guyatt GH, Willan A, Griffith LE. Determining a minimal important change in a disease-specific quality of life questionnaire. J Clin Epidemiol 1994; 47:81-7.
20. Deyo RA, Diehr P, Patrick DL. Reproducibility and responsiveness of health status measures. statistics and strategies for evaluation. Control Clin Trials 1991; 12(4 Suppl):142S-58S.
21. Guyatt GH, Juniper EF, Walter SD, Griffith LE, Goldstein RS. Interpreting treatment effects in randomised trials. BMJ 1998; 316:690-3.
22. Bullinger M, Anderson R, Cella D, Aaronson N. Developing and evaluating cross-cultural instruments from minimum requirements to optimal models. Qual Life Res 1993; 2:451-9.
23. Strinnholm A, Brulin C, Lindh V. Experiences of double-blind, placebo-controlled food challenges (DBPCFC): A qualitative analysis of mothers' experiences. J Child Health Care 2010; 14:179-88.

24. Zijlstra WT, Flinterman AE, Soeters L, et al. Parental anxiety before and after food challenges in children with suspected peanut and hazelnut allergy. Pediatr Allergy Immunol 2010; 21(2 Pt 2):e439-45.
25. Nguyen M, Wainstein BK, Hu W, Ziegler JB. Parental satisfaction with oral peanut food challenges; perception of outcomes and impact on management of peanut allergy. Pediatr Allergy Immunol 2010; 21:1119-26.
26. Kemp AS, Allen CW, Campbell DE. Parental perceptions in egg allergy: Does egg challenge make a difference? Pediatr Allergy Immunol 2009; 20:648-53.
27. Guyatt GH, Osoba D, Wu AW, Wyrwich KW, Norman GR, Clinical Significance Consensus Meeting Group. Methods to explain the clinical significance of health status measures. Mayo Clin Proc 2002; 77:371-83.
28. Schunemann HJ, Akl EA, Guyatt GH. Interpreting the results of patient reported outcome measures in clinical trials: The clinician's perspective. Health Qual Life Outcomes 2006; 4:62.
29. Turner D, Schunemann HJ, Griffith LE, et al. The minimal detectable change cannot reliably replace the minimal important difference. J Clin Epidemiol 2010; 63:28-36.
30. Revicki D, Hays RD, Cella D, Sloan J. Recommended methods for determining responsiveness and minimally important differences for patient-reported outcomes. J Clin Epidemiol 2008; 61:102-9.
31. Wyrwich KW, Tierney WM, Wolinsky FD. Using the standard error of measurement to identify important changes on the asthma quality of life questionnaire. Qual Life Res 2002; 11:1-7.
32. Rejas J, Pardo A, Ruiz MA. Standard error of measurement as a valid alternative to minimally important difference for evaluating the magnitude of changes in patient-reported outcomes measures. J Clin Epidemiol 2008; 61:350-6.
33. DunnGalvin A, Gaffney A, Hourihane JO. Developmental pathways in food allergy: A new theoretical framework. Allergy 2009; 64:560-8.
34. Dunngalvin A, Hourihane JB. Chapter 3 developmental trajectories in food allergy: A review. Adv Food Nutr Res 2009; 56:65-100.

Chapter 8

General discussion and summary

INTRODUCTION

This thesis describes the reliability, longitudinal validity and responsiveness of the FAQLQ-CF, -TF and -AF[1-3] (**chapter 3, 4, 7**) and the cross sectional validation of the FAQLQ-PF and FAQLQ-PFT for use in the Netherlands (**chapter 5, 6**). Additionally, generic and disease-specific HRQL in food allergic patients were compared (**chapter 2**), parent- and self-reports on the patient's HRQL of food allergic children and adolescents were compared (**chapter 5, 6**) and finally, the impact of a DBPCFC and its subsequent changes in management were analyzed (**chapter 7**).

Considering the studies on the psychometric properties of the FAQLQs, this thesis provides for the first time evidence of the good reliability (**chapter 3**), the internal validity (**chapter 2**), longitudinally validity and responsiveness (**chapter 7**) of the FAQLQ-CF, -TF and -AF[1-3]. Additionally, **chapter 5 and 6** provide evidence of the cross-cultural validity of the FAQLQ-PF and PFT. Continuing the previously published findings on the development and the construct validity of the FAQLQs[1-5], this thesis thus presents emerging evidence on the suitability of the FAQLQs as tools capable of measuring self- and parent-reported HRQL of food allergic children, adolescents and adults. Moreover, the FAQLQ-CF, -TF and -AF are the only longitudinally validated and responsive instruments for measuring HRQL in food allergic patients from the patient's perspective. These instruments are thus promising tools for clinical research in which HRQL is the outcome of interest and may help to optimize (future) interventions from a HRQL point of view.

Considering the outcome of the studies presented in this thesis, **chapter 5 and 6** demonstrate that both food allergic children and adolescents differed in their views with their parents on their HRQL. In children, parents systematically reported less impact of food allergy on their child's HRQL then children themselves (**chapter 5**). In contrast to children, differences between adolescent-parent pairs appeared at the individual adolescent-parent pair level rather than at the group level (**chapter 6**). **Chapter 7** showed that children, adolescents and adults benefit from a negative DBPCFC (food allergy ruled out) and its subsequent changes in management and children benefit from a positive DBPCFC. These findings support the large impact of food allergy on HRQL and illustrate which patients benefit from a DBPCFC from a HRQL point of view.

In this final chapter, the findings of this thesis will be summarized and integrated. The first part of this discussion will focus on methodological issues concerning the psychometric properties of the FAQLQs. The second part of this chapter discusses the outcome of the studies in addition to clinical implications and directions for future research.

METHODOLOGICAL ISSUES: PSCYHOMETIRC PROPERTIES OF THE FAQLQS

Chapter 2, 3, 4 and 7 provide insight into the psychometric properties of the FAQLQs. Psychometric properties are important to ensure that the instruments measure what they are supposed to measure and to ensure that they are reproducible over time.

Generic HRQL instruments and the FAQLQs

Health-Related Quality of Life (HRQL) can be measured with generic and disease-specific instruments. Generic and disease-specific questionnaires had never been compared in the same group of food allergic patients. Therefore, **chapter 2** described generic and disease-specific HRQL of food allergic patients. The findings indicated that generic instruments are less sensitive than disease-specific instruments. Although generic HRQL questionnaires are indispensable for the comparison between different diseases, the FAQLQs were more sensitive and consequently were expected to be more suitable to measure clinically important impairments in HRQL (responsiveness). This hypothesis was supported by the findings in **chapter 7**.

Reliability of the FAQLQs

Reliability refers to whether an instrument is dependable and repeatable and can be examined assessing reproducibility (test-retest-reliability). The reproducibility of the FAQLQ-CF, -TF and -AF was assessed in **chapter 3**. Reproducibility was considered to be good with high ICCs and CCCs between 0.907 and 0.976 and mean differences in HRQL that were all close to zero. Therefore, the FAQLQ-CF, -TF and -AF are considered to be reliable tools for group comparisons in clinical trials.

Considering the Bland-Altman plots, it was shown that most of the individual differences in HRQL between the test and re-test lie between the 1.96 SD limits of agreement, supporting the reliability of the FAQLQ-CF, -TF and -AF. However, because the FAQLQ-CF, -TF and -AF have to be able to differentiate between minimal but potentially important changes in clinical status, the limits of agreement must not only be statistically narrow, but also be narrow enough to be clinically meaningful. The smallest difference or change in score associated with a change in health status which patients find important is called the minimal important difference (MID). This minimal important difference is usually around 0.5 in HRQL questionnaires using a seven-point scale[6], but has to be defined yet in following studies assessing responsiveness of the FAQLQ-CF, -TF and -AF. An initial estimate can be made, using the MID as limits of agreement (mean difference +/- 0.5 MID), showed that 77% of the differences for the FAQLQ-CF, 91% for FAQLQ-TF and 78% for FAQLQ-AF lie within these limits. Since a relatively small percentage of test-retest variability is in the range that patients find clinically important, we think the FAQLQ-

CF, -TF and -AF have sufficient interpretability to yield meaningful information in group comparisons in clinical trials.

In order to assess whether a newly developed instrument is also a reliable tool for monitoring individual patients specific criteria are needed. To our knowledge, only one study was available on the criteria for monitoring individual patients at the start of the study described in this thesis[7]. For monitoring individual patients reliability should be higher (ICC/CCC > 0.90-0.95) than for group comparisons in clinical trials (ICC/CCC > 0.7)[7]. Additional criteria for the application of instruments for individual patients are a small standard error of measurement and the usual qualities such as construct validity and sensitivity to clinical change. Since reliability statistics were above 0.90 (**chapter 3**), the standard error of measurement was relatively small (FAQLQ-AF=0.25, FAQLQ-TF=0.16, and FAQLQ-CF=0.44) (**chapter 7**), minimal floor and ceiling effects were shown (**chapter 2**) and construct validity[1-3] (**chapter 4**) and sensitivity to clinical change (**chapter 7**) has been shown, the FAQLQs are promising tools for monitoring individual patients.

Another theory has recently been proposed for assessing whether an instrument is suitable for monitoring individual patients using qualitative methods rather than statistical methods assessing psychometric properties of questionnaires[8]. In this methodology the focus of interest to be measured (i.e. HRQL) should be fully assessed by an in-depth interview[9]. Additionally, this 'reality' as measured by the in depth interview may be used as the gold standard and should be correlated with the patient's score on the questionnaire. When there is good agreement this supports the suitability of the instruments for monitoring individual patients. The use of qualitative methods to assess the individual accuracy of a questionnaire in routine practice may provide additional insight into the suitability of an instrument for monitoring individual patients in addition to statistical methods.

Thus, considering the reliability and other psychometric properties of the FAQLQ-CF, -TF and -AF, these instruments are suitable tools for group comparisons in clinical trials and promising tools for monitoring HRQL in individual patients. However, it would be informative to further evaluate their feasibility in daily clinical practice before these tools are used for monitoring individual patients.

Validity of the FAQLQs

The validity of an instrument refers to the instruments ability to measure what it is supposed to measure. **Chapter 4 and 7** are related to the validation of the FAQLQs and continue the studies on the cross-sectional validation of the FAQLQ-CF, -TF and -AF published by Flokstra-de Blok et al.[1-3]. **Chapter 4** described the instrument used for validating the FAQLQs and **chapter 7** described the longitudinal validity of the FAQLQs. During the validity process of the FAQLQs some issues were encountered, which are common in HRQL research. These issues will be discussed below.

The first issue we encountered was that a new instrument is usually compared to the true value, a gold-standard, to make it plausible that the new instrument is valid (criterion validity). However, in HRQL research no such a gold standard exists to which a new HRQL questionnaire could be compared. Thus, other methods (and other instruments) are needed to validate a new HRQL questionnaire. In HRQL research, the best way to assess validity is called construct validity. Construct validity is assessed by correlating the HRQL questionnaire with an independent measure which reflects the severity of the disease in question in order to validate the disease-specificity of the HRQL questionnaire. Thus, in order to validate the FAQLQs, an appropriate food allergy independent measure was needed.

The second issue we encountered was the fact that no appropriate independent measure existed in food allergy that could be used in order to assess construct validity of the FAQLQs in terms of disease-specificity. Therefore **chapter 4** described the development of a new instrument, the Food Allergy Independent Measure (FAIM), consisting of items reflecting several aspects of the severity of disease such as risks of outcome of a food allergic reactions following exposure, more objective aspects of severity of disease, such as the number of products that should be avoided, and more social aspects of severity of disease. The development of the FAIM was built upon the method of expectation of outcome[10]. This approach has been successfully implemented to validate disease-specific HRQL instruments[11,12]. Face validity and relevance of the developed FAIM items were determined by expert opinion. FAIM items were considered valid if they addressed aspects of food allergy outcomes that patients were likely to perceive as determining the severity of their condition. FAIM items showing no correlation to any potential FAQLQ item were not considered relevant and therefore eliminated. Overall, the face validity, relevance and the reliability of the FAIMs were shown to be good. Therefore the final FAIMs were considered to be suitable instruments for validating the FAQLQs.

The third difficulty in measuring construct validity was the fact that there is no real guideline in literature on what correlations should be expected between an independent measure and a newly developed HRQL instruments, because such correlations depend on several factors such as the disease studied and the type of independent measure that is used. Additionally, there are multiple other factors influencing HRQL. It has previously been suggested that such correlations should be moderate[13]. Therefore, we hypothesized that moderate correlations were to be expected between the FAQLQ and the FAIM. This hypothesis was supported by previous findings of studies using HRQL instruments that were validated using comparable independent measures built upon the methods of expectation of outcome questions. These studies showed correlations between HRQL and expectation of outcome at baseline measurement of 0.41 and 0.59 for the Food Allergy Quality of Life Parental Burden questionnaire (FAQL-PB, 2004)[11] and the Vespid Allergy Quality of Life Questionnaire (VAQLQ, 2002)[12], respectively.

In **chapter 5 and 6**, the cross cultural validity of the FAQLQ-PF and -PFA was assessed by correlating the FAQLQ with the FAIM. Correlations of 0.58 and 0.64, respectively, were shown, supporting the cross-cultural validity of these instruments. Longitudinal validity was assessed **in chapter 7** by measuring correlations between the change [baseline minus follow-up] in FAQLQ scores and the change in FAIM scores. Higher correlations were shown for adults (0.71), than for children (0.50) and adolescents (0.35). The longitudinal validity of the adult-form (FAQLQ-AF) was comparable to the longitudinal validity of other HRQL instruments completed by adults: for the VAQLQ, a correlation of 0.72 was shown[12] and for the FAQLQ-PF, correlations were ranging from 0.65-0.74[14]. The finding that higher correlations were shown for adults than for children and adolescents may suggest that the longitudinal validity of the FAQLQ-AF is better than the longitudinal validity of the FAQLQ-CF and -TF. However, this may also reflect age-related differences in factors determining changes in health-related quality of life in food allergic patients. The influence of such factors determining HRQL changes needs further investigation. Since moderate to good correlations were shown between the change in FAQLQs and FAIMs and because all FAQLQs were able to measure statistically and clinically relevant changes, we feel the FAQLQs have sufficient longitudinal validity to yield meaningful information in group comparisons in clinical trials.

Thus, measuring construct validity is a lengthy and ongoing process of learning more about the construct, making new predictions and then testing them. Each study that supports the theoretical construct strengthens the theory. Our results support the reliability, relevance and validity of the independent measure, the FAIM **(chapter 4)**. Additionally, our results support the reliability **(chapter 3)** and the cross-sectional validity of the FAQLQ-CF, -TF and -AF[1,3] and the cross cultural validity of the FAQLQ-PF and -PFA**(chapter 5 and 6)**. **Chapter 7** supported the longitudinal validity and the ability of the FAQLQ-CF, -TF and -AF to measure change over time. These studies thus support the suitability of the FAQLQs for measuring HRQL in food allergic patients. This would not have been the case if establishing construct validity of the FAQLQs with an expectation of outcome measure was somehow invalid or tautological.

Responsiveness of the FAQLQs and relevant differences in HRQL

The responsiveness of a newly developed instrument refers to the ability of the instrument to measure relevant changes. The responsiveness of the FAQLQ-CF, -TF and -AF is described in **chapter 7**. Currently, there is much discussion in literature on the definition of a relevant change. Although HRQL measurements are increasingly being used as outcome measure, results are not always analyzed and interpreted identically[15-19], because there are different methods to assess the relevance of HRQL differences. Distribution-based or anchor-based methods can be used to determine the change in HRQL that is considered relevant (the minimal important difference, MID). Distribution-based methods, such as Cohen's effect

size or SEM, rely on scoring methods of an instrument and the distribution of the results[17]. The SEM, which is not sample dependent, has been proposed as a method of relevance to MID estimation, because a SEM change often corresponds well to an anchor-based MID change of 0.5 on a seven-point response scale[20 22]. However, distribution-based methods provide no information regarding the importance of the change; i.e. although the magnitude of the change may certainly be significant, it is not necessarily meaningful to patients.

Anchor-based methods use an external criterion (anchor) to interpret whether a particular magnitude of change is meaningful for patients/clinicians. The global rating of change questionnaire[19] is often used as an anchor and contains broadly evaluative questions to examine overall HRQL-changes and to classify patients according to whether their HRQL has improved or deteriorated. A disadvantage of global rating of change may be that patients are unable to accurately recall their initial health status which causes global measures of change to be highly correlated with the current state and uncorrelated with the initial state[20]. As it is necessary to know whether the observed change is important from the patient's/clinician's perspective, anchor-based methods are still preferred in assessing the MID[19]. Distribution-based methods can be used when anchor-based estimates are unavailable[18] or to support estimates from anchor-based methods.

Another method to improve the evaluation of the relevance of a HRQL change, is to compare the HRQL change in the intervention group with the HRQL change of a control group. This overall differences (change in HRQL following DBPCFC minus change in HRQL in the control group) should exceed the MID/SEM. Additionally, the use of a control group allows calculation of the number needed to treat (NNT)[15, 23], representing the number of patients that need to be treated for one patient to have a clinically important improvement in HRQL. It is our considered opinion that this approach is the best way to evaluate whether the change in HRQL score of an intervention is clinically significant. Therefore, we recommend a combination of these methods to assess the clinical relevance of HRQL changes.

In **chapter 7**, this combined approach was used to investigate whether the HRQL change following DBPCFC was relevant for children, adolescents and adults. It was shown that the FAQLQ-CF, -TF and -AF were all able to measure relevant changes in HRQL. Consequently, our results support the responsiveness of the FAQLQ-CF, -TF and -AF.

OUTCOME OF THIS THESIS

HRQL following DBPCFC

Chapter 7 showed that adults, adolescents and children benefit from a negative DBPCFC and its subsequent changes in management. Children also benefit if the outcome is positive. These findings are in line with previous studies[14, 24-28]. The improvement in HRQL

following a negative DBPCFC was significantly greater than the change in HRQL of the control group and this overall improvement exceeded the MID as well as the SEM after correction for confounding. The NNT of a negative DBPCFC was 4 for all age-groups. Thus, for every 4 participants who have a negative DBPCFC 1 participant has a clinically important improvement in HRQL. These findings thus support the large impact of food allergy on HRQL and the clinical effectiveness of a DBPCFC and its subsequent changes in management. Following a positive DBPCFC the NNT was 4 for children and 8 for adults.

Other studies describing the impact of interventions on HRQL in allergic disorders showed NNTs between 1.4 and 14: The NNT of Levocetirizine as ad-on therapy to Fluctiasone was shown to be 14 in patients suffering from seasonal allergic rhinitis[29]. The NNT of Montelukast compared to placebo was shown to be 9 in children (2-5 years old) with intermittent asthma[30]. The NNT of Omalizmab as add-on therapy to high-dose inhaled corticosteroids and long acting b2-agonists was shown to be 7.6 in patients with severe persistent asthma[31]. The NNT of venom immunotherapy compared to epinephrine auto-injector was shown to be 1.4-1.7 in patients suffering from jellow jacket venom allergy[32]. We found an NNT of 4 following a DBPCFC compared to a control group (following a negative outcome: all ages, following a positive outcome: children only). Comparing our results to the results described above, a DBPCFC was considered to be a relevant intervention for these specified groups. An NNT of a positive DBPCFC of 8 for adults can be considered to be intermediate compared to other published results. Our findings thus provide clinicians with an additional reason to perform a DBPCFC in food allergic patients from a HRQL point of view.

Differing views of food allergic patients and their parents on the patient's HRQL

Chapter 5 and 6 describe differing views of food allergic children/adolescents and their parents on the patient's HRQL. **Chapter 5** demonstrated that children (8-12 years) systematically reported a significantly greater impact of food allergy on their HRQL than their parents, whereas child- and parent-reported perception of disease severity, expectation of outcome of an allergic reaction and the psychometric properties of the FAQLQ-CF and -PF were nearly identical. **Chapter 6** illustrated that relevant differences between adolescents and their parents appeared at the individual adolescent-parent pair level (for 63% of all adolescent-parent pairs) rather than at the group level. Although a trend was shown in the direction of a systematic underestimation of parents on the adolescent's HRQL (parents 3.56 versus adolescents 3.78, p=0.103), this difference was not statistically or clinically significant.

When interpreting the outcome of **chapter 5 and 6**, it is important to notice that the relevance of the difference between child- and parent-reported HRQL depends on whether the questionnaires are intended to be used to provide substitute or complementary data on the patient's HRQL[33]. The term 'substitute perspective' is used when the parent-

report is used as a proxy-report to provide a substitute for the child's response (FAQLQ-PF for children aged 0-8 years). The term 'complementary perspective' is used when both a parental and a child report are used and to provide additional insight into the child's HRQL (FAQLQ-PF for children aged 8-12 years and FAQLQ-PFA for adolescents aged 13-17 years). As HRQL is concerned with an individual's perception, self-reports are the primary method of assessment and instruments developed to provide a substitute perspective do need to reflect the child's experience accurately. Therefore, the extent of agreement between child- and parent-reports indicates the validity of the parental response as a proxy measure. **Chapter 5** showed that child-parent correlation was moderate (ICC=0.57) and that children systematically reported a significantly greater impact of food allergy on their HRQL than their parents. This suggests a moderate validity of the parental response as a proxy-measure and it is important to know that in situations in which a child is unable to complete a self-report, the parent is likely to underestimate the deterioration of the child's HRQL as measured with the FAQLQ-PF.

A second important subject to notice when interpreting the outcome of **chapter 5 and 6**, is the phenomenon that apparent agreement does not necessarily represent true concordance[33]. This can be noticed in **chapter 6**, where moderately good correlations (ICC=0.61) and no significant differences were shown between the parent and adolescent-report, which may indicate relatively good agreement. However, Bland-Altman plots illustrated that relevant differences between adolescent-parent pairs appeared for 63% of all individual adolescent-parent pairs. This illustrates that agreement may be poorer than it initially seems to be.

The findings of moderate child-parent agreement and moderate adolescent-parent agreement on the patient's HRQL are perhaps not surprising. From a clinical point of view, it is most interesting what the direction of the difference is and why there is a difference. We identified some factors that were associated with such disagreement on HRQL as will be described in the next section.

Emerging insight in factors associated with HRQL in food allergic patients

As mentioned in **Chapter 1**, HRQL is a multidimensional concept, a dynamic concept and a concept that is influenced by several factors. Although it was not the main aim of this thesis to identify which factors predict HRQL, some interesting results regarding this topic were identified. Therefore, factors associated with HRQL will be summarized and discussed below.

Factors associated with HRQL in food allergic children, adolescents and adults

Chapter 2 describes some factors associated with food allergy related quality of life. The FAIM was shown to have the strongest association with HRQL in children, adolescents and adults. Thus, risk perception and expectations on the outcome following accidental

exposure are substantial predictors of HRQL. Less prominent predictors were severity of symptoms and number of food allergies. The type of food allergy showed no association with HRQL at all. These findings underline our previously mentioned hypotheses that objective parameters in food allergy are not as closely linked to HRQL of food allergic patients as risk perceptions and expectations regarding the outcome of an allergic reaction following accidental exposure. It is rather the risk of food reactions and measures to avoid them that are associated with lower HRQL than the clinical reactivity induced by food intake[34]. Thus, HRQL is determined not only by the patient's health status problems but also by their response and interpretation of their health status problems.

Factors associated with patient-parent disagreement on HRQL of food allergic children and adolescents

Chapter 5 and 6 describe factors associated with patient-parent disagreement on the patient's HRQL. Disagreement between child- and parent-proxy-reports may reflect real differences in perspectives of children and parents and may relate to several factors. Firstly, patient-parent disagreement on the patient's HRQL was related to the age of children and adolescents. It was shown that child-parent agreement was highest for food allergic children aged 11-15 years **(chapter 5 and 6)**. Secondly, higher perceived disease severity (FAIM-TF) contributed significantly to a larger difference between adolescent- and parent-reported HRQL (in line with **chapter 2**). Another factor associated with larger adolescent-parent disagreement was poorer adolescent-reported perceived illness comprehension. Overall, adolescent-reported illness perceptions and expectations showed stronger associations with the mean difference on HRQL than parent-reported illness perceptions and expectations, which suggests that most determinants of the adolescent's HRQL are poorly perceived by their parents.

A recently published study on adolescent-parent disagreement on the adolescent's HRQL in chronically ill adolescents[35] confirmed our findings. It was shown that adolescent-parent disagreement on the adolescent's HRQL was associated with factors such as experienced disease burden, a higher adolescent age (15.3 years old versus 14.8 years old) and a lower educational level of the adolescent. It would be interesting to study whether an education program for adolescents may improve the adolescent's understanding of food allergy, the adolescent's HRQL and consequently, adolescent-parent disagreement on the adolescent's HRQL.

Factors associated with the impact of a DBPCFC on HRQL in food allergic patients

Chapter 7 describes the impact of a DBPCFC and its subsequent changes in management on HRQL. Although it was not the main aim of this study, some findings were presented on factors associated with the impact of a DBPCFC on HRQL. Firstly, the outcome of the DBPCFC was associated with change in HRQL (i.e. larger improvements in HRQL were

shown following a negative outcome than following a positive outcome). Additionally, having more than two food allergies was associated with deterioration in HRQL following a DBPCFC for children. Finally, higher FAQLQ baseline scores (poorer HRQL) contributed significantly to improvement in HRQL for all ages. Another small subgroup analysis was performed on participant characteristics that tended to be more common in participants whose HRQL deteriorated following a negative DBPCFC compared to participants whose HRQL did not deteriorate. These factors are number of food allergies, percentage of peanut challenges, percentage of participants who did not eat the tested food despite the negative DBPCFC. These factors may influence deterioration in HRQL following a negative challenge. However, this needs further investigation with larger numbers of patients.

There are a few other studies describing factors influencing the impact of a food challenge on HRQL[24-28]. Some distressing factors influencing the impact of a food challenge were seeing their child fall ill (following a positive outcome), inconclusive outcome and continuing uncertainty, difficulties in getting their child to consume peanut during the challenge, inadequate follow-up and distress during intravenous cannula insertion[25]. Dunn Galvin et al. showed some additional distressing factors such as a positive outcome of the food challenge, a high HRQL baseline score (worse HRQL), high level of FAIM (high risk perception), recent experience of anaphylaxis, more severe symptoms and having more food allergies[14]. Remarkably, severity of the reaction during the challenge was not a significant predictor[14]. Additionally, another study illustrated that during the challenge, the experience of a previous allergic reaction was related to parental state anxiety and two weeks after the challenge, the outcome of the DBPCFC was related to state anxiety[28]. The most distressing factor that appeared following reintroduction of a food after a negative DBPCFC in food allergic children (as perceived by their mothers), was fear of living with the unknown including feelings of fear of losing control and causing harm[26]. Some factors positively influencing HRQL following a food challenge were also identified. These factors were clarification of the severity of the child's peanut allergy, support provided by staff and determining the child was tolerant of peanut or assessed to be at low risk of anaphylaxis from accidental exposure[25]. It would be interesting to further analyze which factors predict HRQL changes following a DBPCFC using the FAQLQs in order to identify targets aimed at improving HRQL of food allergic patients following a DBPCFC.

IMPLICATIONS FOR CLINICAL PRACTICE

The studies in this thesis have several implications for clinical practice. Firstly, the studies in this thesis present for the first time evidence of the reliability **(chapter 3)**, longitudinally validity, responsiveness **(chapter 7)** and cross cultural validity **(chapter 5 and 6)** of instruments capable of measuring self- and parent-reported HRQL of food allergic children, adolescents and adults. As there are no other clinical instruments for measuring

the ongoing impact of food allergy, the FAQLQs are suitable tools for measuring the impact of future interventions such as immunotherapy on HRQL of food allergic patients. Information from the FAQLQs may help to optimize interventions from a HRQL point of view.

Secondly, we evaluated the impact of a DBPCFC from a HRQL point of view **(chapter 7)** and it was shown that children, adolescents and adults benefit from a negative DBPCFC and children (and to a lesser extent adult) benefit from a positive DBPCFC. As a DBPCFC is considered to be a time-consuming process and has previously been discussed in the literature as being potentially burdensome to patients, it is important for clinicians to know that a DBPCFC is not only the gold standard for diagnosing food allergy, but also improves HRQL for specified groups. This message is of interest to all health-care professionals who deal with food allergic patients as it provides them with an additional reason to invest the time and effort to offer these patients DBPCFCs where appropriate.

Thirdly, it is important for clinicians to know that self- and parent-reports on the child's HRQL differ, in which direction the difference is and which factors are associated with such disagreement **(chapter 5 and 6)**. As parental attitudes may influence the utilization of health-care services for their child and may indirectly influence clinical decision making, it is important to keep in mind that parents tend to underestimate the deterioration of their child's HRQL (8-12 years) and that adolescent-parent pairs differed in their views on the adolescent's HRQL on the individual adolescent-parent pair level (13-17 years). It is thus recommended to include both opinions of parents and patients in clinical decision making in order to make a complete assessment of the impact of food allergy and related interventions on HRQL.

Regarding the determinants of such disagreement, it was shown that illness comprehension of the adolescent was associated with adolescent-parent disagreement on the adolescent's HRQL. As already mentioned, this may be an important target for intervention aimed at improving the adolescent's understanding of food allergy and consequently the adolescent's HRQL.

Fourthly, in addition to differing views between adolescents and parents on the adolescent's HRQL **(chapter 6)**, it was also shown that the adolescent's perspective on HRQL (and determinants of HRQL) differed from the child's and the adult's perspective in several ways. At first, it was shown that the content of the FAIM of adolescents differed from the FAIM of children and adults: the item "how big do you think the chance is that you will die if you accidentally eat something to which you are allergic?" was considered to be inappropriate for adolescents in contrast to children, adults **(chapter 4)** and parents of food allergic children[4], because this item did not correlate with any of the FAQLQ-TF items. This might indicate that adolescents are not afraid of dying of anaphylaxis and underestimate exposure in contrast to adults and children. Secondly, adolescent's did not improve in HRQL following a positive DBPCFC, in contrast to children and adults. Thirdly, adolescents in the control group showed a statistical (but not a clinical) improvement in

their HRQL in contrast to children and adults **(chapter 7)**. In line with previous findings[36], above results indicate that (determinants of) HRQL may well be age-related. Consequently, it is important for clinicians to realize that it is highly likely that targets aimed at improving HRQL of food allergic adolescents may differ from children and adults as well.

Finally, this thesis illustrated the importance of patient-reported outcomes to get insight into aspects of food allergy considered important by patients. It was shown that some aspects of food allergy that are generally considered important by clinicians (severity of symptoms, number of food allergies and type of food allergy) had weaker associations with the patient's HRQL than patient's risk perceptions and expectations regarding the outcome of an allergic reaction (FAIM) **(chapter 2)**. These findings confirmed previously published studies that HRQL of food allergic patients is determined not only by the patient's health status problems but also by their response and interpretation of their health status problems[37]. Information from patient-reported outcomes may improve the ability of health-care professionals to help food allergic patients with managing their specific problems in order to improve the patient's HRQL.

FUTURE PERSPECTIVES

Although this thesis outlines the current knowledge regarding food allergy and HRQL, there are still many unanswered and interesting research questions that need further investigation. Some of them are mentioned below.

Regarding the psychometric properties of the FAQLQs, the first important issue to analyze is the assessment of the minimal important difference (MID). Assessment of the MID is useful, because it will enhance our understanding of the interpretation of the relevance of changes as measured by the FAQLQs. Currently, the MID of the FAQLQs is unknown. Therefore, this needs further investigation using methods described earlier in this thesis.

A second issue involves the validation of the FAQLQs in other countries and languages. Before the FAQLQ-CF, -TF and -AF can be used in other languages and cultures the questionnaires should be cross-culturally validated in the new language or culture, because some items generated and selected in one culture may not always be considered important in other cultures. Cross cultural validation involves several phases such as forward and backward translations and cross sectional validation, after which the FAQLQs can be incorporated into a longitudinal study in the new language. It would be interesting to compare self- and parent-reported HRQL of food allergic patients in several countries.

A third issue regarding the psychometric properties of the FAQLQs is related to the suitability of the FAQLQs as tool for monitoring individual patients. The FAQLQs have shown to be suitable tools for group comparison studies. Although the FAQLQs fulfilled the available psychometric criteria for monitoring individual patients, it is recommended to further analyze the suitability of the FAQLQs for this purpose.

In addition to research questions regarding the psychometric properties of the FAQLQs, some other research questions can be mentioned. This thesis identified some factors that were associated with HRQL. However, which factors influence HRQL remains largely unknown and it would be interesting to find out which factors predict HRQL in order to identify targets aimed at improving HRQL of food allergic patients. In line with this research question, it would be interesting to identify which factors predict change in HRQL following a DBPCFC in order to answer questions such as why some patients deteriorate following a negative food challenge and why adolescents perceive a positive outcome differently than adults and children. Some determinants may be targets for intervention aimed at improving the patient's HRQL following a DBPCFC.

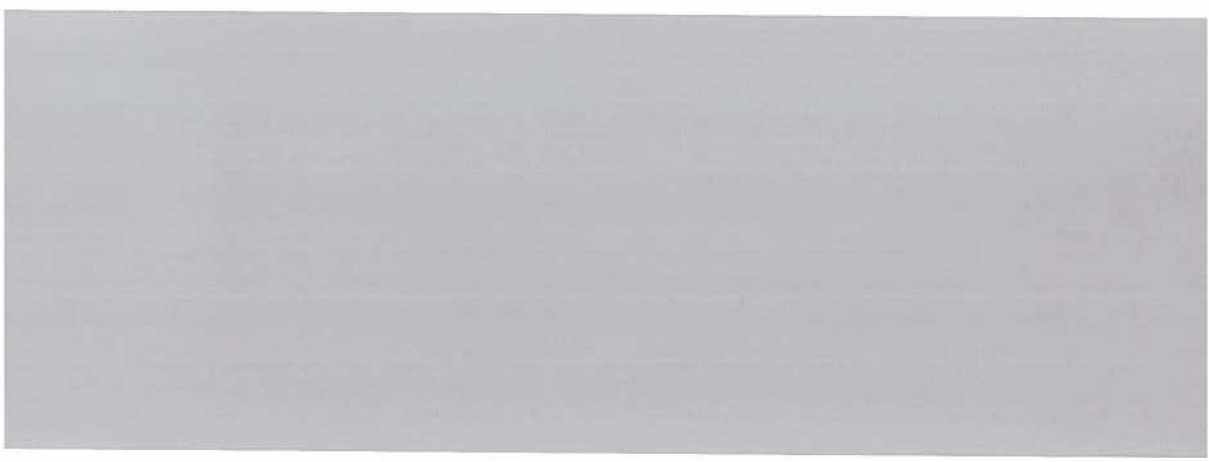
Additionally, it would be interesting to further analyze the association between the adolescent's illness comprehension and adolescent-parent disagreement on the adolescent's HRQL and the hypothetical association with self-management. An education program may be a useful target for intervention aimed at improving the knowledge of adolescents on their food allergy, the adolescent's HRQL, adolescent-parent disagreement on HRQL and possibly self-management. Although, there is growing interest in food allergic adolescents and HRQL[38,39], these questions are still unanswered.

Finally, it would be interesting to compare HRQL outcome with economic measurements developed in the Europrevall project. The economic instruments were developed to measure the economic impact of food allergy. It would be interesting to investigate whether socio-emotional impact of food allergy is related to the economic impact of food allergy.

REFERENCE LIST

1. Flokstra-de Blok BM, DunnGalvin A, Vlieg-Boerstra BJ, et al. Development and validation of a self-administered food allergy quality of life questionnaire for children. Clin Exp Allergy 2009; 39:127-37.
2. Flokstra-de Blok BM, DunnGalvin A, Vlieg-Boerstra BJ, et al. Development and validation of the self-administered food allergy quality of life questionnaire for adolescents. J Allergy Clin Immunol 2008; 122:139-44, 144.e1-2.
3. Flokstra-de Blok BM, van der Meulen GN, DunnGalvin A, et al. Development and validation of the food allergy quality of life questionnaire - adult form. Allergy 2009; 64:1209-17.
4. DunnGalvin A, de BlokFlokstra BM, Burks AW, Dubois AE, Hourihane JO. Food allergy QoL questionnaire for children aged 0-12 years: Content, construct, and cross-cultural validity. Clin Exp Allergy 2008; 38:977-86.
5. Hamp N, Hourihane J, Knibb RC, Dubois AEJ, Flokstra-de Blok BMJ, DunnGalvin A. Developmental specificity and sensitivity between two age appropriate health-related quality of life measures in food allergic children and teenagers. J Allergy Clin Immunol 2008; 121:S107.
6. Juniper EF, Guyatt GH, Jaeschke R. How to develop and validate a new health-related quality of life instrument. In: Spilker B, ed. Quality of life and pharmacoeconimcs in clinical trials. Philadelphia: Lippincott-Raven Publishers; 1996. p. 49-56.
7. McHorney CA, Tarlov AR. Individual-patient monitoring in clinical practice: Are available health status surveys adequate? Qual Life Res 1995; 4:293-307.
8. Kocks JW, Kerstjens HA, Snijders SL, et al. Health status in routine clinical practice: Validity of the clinical COPD questionnaire at the individual patient level. Health Qual Life Outcomes 2010; 8:135.
9. van der Molen T, Kocks JW. Do health-status measures play a role in improving treatment in chronic obstructive pulmonary disease? Expert Opin Pharmacother 2006; 7:57-61.
10. Oude Elberink JN. Significance and rationale of studies of health-related quality of life in anaphylactic disorders. Curr Opin Allergy Clin Immunol 2006; 6:298-302.
11. Cohen BL, Noone S, Munoz-Furlong A, Sicherer SH. Development of a questionnaire to measure quality of life in families with a child with food allergy. J Allergy Clin Immunol 2004; 114:1159-63.
12. Oude Elberink JN, de Monchy JG, Golden DB, Brouwer JL, Guyatt GH, Dubois AE. Development and validation of a health-related quality-of-life questionnaire in patients with yellow jacket allergy. J Allergy Clin Immunol 2002; 109:162-70.
13. Bullinger M, Anderson R, Cella D, Aaronson N. Developing and evaluating cross-cultural instruments from minimum requirements to optimal models. Qual Life Res 1993; 2:451-9.
14. DunnGalvin A, Cullinane C, Daly DA, Flokstra-de Blok BM, Dubois AE, Hourihane JO. Longitudinal validity and responsiveness of the food allergy quality of life questionnaire - parent form in children 0-12 years following positive and negative food challenges. Clin Exp Allergy 2010; 40:476-85.
15. Guyatt GH, Osoba D, Wu AW, Wyrwich KW, Norman GR, Clinical Significance Consensus Meeting Group. Methods to explain the clinical significance of health status measures. Mayo Clin Proc 2002; 77:371-83.
16. Schunemann HJ, Akl EA, Guyatt GH. Interpreting the results of patient reported outcome measures in clinical trials: The clinician's perspective. Health Qual Life Outcomes 2006; 4:62.
17. Turner D, Schunemann HJ, Griffith LE, et al. The minimal detectable change cannot reliably replace the minimal important difference. J Clin Epidemiol 2010; 63:28-36.
18. Revicki D, Hays RD, Cella D, Sloan J. Recommended methods for determining responsiveness and minimally important differences for patient-reported outcomes. J Clin Epidemiol 2008; 61:102-9.
19. Juniper EF, Guyatt GH, Willan A, Griffith LE. Determining a minimal important change in a disease-specific quality of life questionnaire. J Clin Epidemiol 1994; 47:81-7.
20. Norman GR, Sloan JA, Wyrwich KW. Interpretation of changes in health-related quality of life: The remarkable universality of half a standard deviation. Med Care 2003; 41:582-92.
21. Wyrwich KW, Tierney WM, Wolinsky FD. Using the standard error of measurement to identify important changes on the asthma quality of life questionnaire. Qual Life Res 2002; 11:1-7.
22. Rejas J, Pardo A, Ruiz MA. Standard error of measurement as a valid alternative to minimally important difference for evaluating the magnitude of changes in patient-reported outcomes measures. J Clin Epidemiol 2008; 61:350-6.
23. Guyatt GH, Juniper EF, Walter SD, Griffith LE, Goldstein RS. Interpreting treatment effects in randomised trials. BMJ 1998; 316:690-3.

24. Kemp AS, Allen CW, Campbell DE. Parental perceptions in egg allergy: Does egg challenge make a difference? Pediatr Allergy Immunol 2009; 20:648-53.
25. Nguyen M, Wainstein BK, Hu W, Ziegler JB. Parental satisfaction with oral peanut food challenges; perception of outcomes and impact on management of peanut allergy. Pediatr Allergy Immunol 2010; 21:1119-26.
26. Strinnholm A, Brulin C, Lindh V. Experiences of double-blind, placebo-controlled food challenges (DBPCFC): A qualitative analysis of mothers' experiences. J Child Health Care 2010; 14:179-88.
27. Knibb RC, Ibrahim NF, Stiefel G, et al. The psychological impact of diagnostic food challenges to confirm the resolution of peanut or tree nut allergy. Clin Exp Allergy 2012; 42:451-9.
28. Zijlstra WT, Flinterman AE, Soeters L, et al. Parental anxiety before and after food challenges in children with suspected peanut and hazelnut allergy. Pediatr Allergy Immunol 2010; 21(2 Pt 2):e439-45.
29. Barnes ML, Ward JH, Fardon TC, Lipworth BJ. Effects of levocetirizine as add-on therapy to fluticasone in seasonal allergic rhinitis. Clin Exp Allergy 2006; 36:676-84.
30. Bisgaard H, Zielen S, Garcia-Garcia ML, et al. Montelukast reduces asthma exacerbations in 2- to 5-year-old children with intermittent asthma. Am J Respir Crit Care Med 2005; 171:315-22.
31. Humbert M, Beasley R, Ayres J, et al. Benefits of omalizumab as add-on therapy in patients with severe persistent asthma who are inadequately controlled despite best available therapy (GINA 2002 step 4 treatment): INNOVATE. Allergy 2005; 60:309-16.
32. Oude Elberink JN, De Monchy JG, Van Der Heide S, Guyatt GH, Dubois AE. Venom immunotherapy improves health-related quality of life in patients allergic to yellow jacket venom. J Allergy Clin Immunol 2002; 110:174-82.
33. Smith H. Differing views of children and parents: Some cautionary tales! Clin Exp Allergy 2011; 41:1344-5.
34. Marklund B, Ahlstedt S, Nordstrom G. Health-related quality of life in food hypersensitive schoolchildren and their families: Parents' perceptions. Health Qual Life Outcomes 2006; 4:48.
35. Sattoe JN, van Staa A, Moll HA, On Your Own Feet Research Group. The proxy problem anatomized: Child-parent disagreement in health related quality of life reports of chronically ill adolescents. Health Qual Life Outcomes 2012; 10:10.
36. Wassenberg J, Cochard MM, Dunngalvin A, et al. Parent perceived quality of life is age-dependent in children with food allergy. Pediatr Allergy Immunol 2012; 23:412-9.
37. Flokstra-de Blok BM, Dubois AE. Quality of life in food allergy: Valid scales for children and adults. Curr Opin Allergy Clin Immunol 2009; 9:214-21.
38. Resnick ES, Pieretti MM, Maloney J, Noone S, Munoz-Furlong A, Sicherer SH. Development of a questionnaire to measure quality of life in adolescents with food allergy: The FAQL-teen. Ann Allergy Asthma Immunol 2010; 105:364-8.
39. Mackenzie H, Roberts G, Van Laar D, Dean T. A new quality of life scale for teenagers with food hypersensitivity. Pediatr Allergy Immunol 2012; 23:404-11.



WAT IS VOEDSELALLERGIE?

Voedselallergie is een veelvoorkomende ziekte in de westerse wereld en komt voor bij ongeveer 6-8% van de kinderen en 3-4% van de volwassenen. Bij een voedselallergie is er sprake van een abnormale reactie van het afweersysteem op het eten van bepaalde voedingsmiddelen. Ieder voedingsmiddel kan voedselallergie veroorzaken, maar de meest voorkomende voedingsmiddelen die voedselallergie veroorzaken zijn pinda, noten, ei, melk, tarwe, vis, sesam, groente en fruit. Een allergie voor melk of ei verdwijnt vaak naarmate iemand ouder wordt, maar een allergie voor pinda of noten heeft een patiënt meestal levenslang. Voedselallergie kan huid-, maag-, darm- of luchtwegklachten veroorzaken. In het ergste geval kan een patiënt in een shock raken en overlijden. De ernst van een allergische reactie kan erg variëren en een patiënt met alleen een milde allergische reactie in het verleden kan soms een levensbedreigende allergische reactie krijgen wanneer hij of zij opnieuw wordt blootgesteld aan hetzelfde voedingsmiddel. Soms kan slechts een hele kleine hoeveelheid van het voedingsmiddel al leiden tot een ernstige allergische reactie.

De enige behandeling voor voedselallergie is strikte vermijding van de voedingsmiddelen waar hij of zij allergisch voor is. Toch bestaat er altijd nog een kans dat iemand het voedingsmiddel waar hij of zij allergisch voor is binnenkrijgt met als mogelijk gevolg een ernstige allergische reactie. Deze onzekerheid en onvoorspelbaarheid van voedselallergie kan angstklachten veroorzaken. Goede diagnostiek en voorlichting is daarom erg belangrijk, zodat een patiënt goed weet welke voedingsmiddelen wel en niet gebruikt mogen worden en hoe en in welke gevallen noodmedicatie (een adrenaline-pen) gebruikt moet worden. In het dagelijkse leven lopen patiënten vaak tegen verschillende problemen aan. Het is bijvoorbeeld belangrijk dat patiënten met een voedselallergie continu alert zijn op wat ze eten. Patiënten zijn dus genoodzaakt om etiketten van voedselproducten goed te lezen. Dit kan soms veel frustratie opleveren, bijvoorbeeld door slechte of onvolledige etikettering van voedselproducten of wanneer ingrediënten van deze producten wijzigen. Daarnaast kan het hebben van een voedselallergie onrust veroorzaken wanneer de patiënt het gevoel heeft dat andere mensen onvoldoende rekening houden met de voedselallergie, zoals in een restaurant of als andere mensen voor ze koken of met traktaties in de klas en schoolfeestjes. Zo zijn er nog veel meer voorbeelden te noemen. Logischerwijs kunnen bovengenoemde factoren invloed hebben op de kwaliteit van leven van patiënten met voedselallergie.

WAT IS KWALITEIT VAN LEVEN?

Kwaliteit van leven is een heel breed begrip en er zijn daarom ook heel veel verschillende definities van dit begrip. Meestal wordt kwaliteit van leven omschreven als het fysieke,

psychische en sociale functioneren van iemand en de subjectieve evaluatie daarvan. Het staat dus centraal wat iemand zelf van zijn of haar fysieke, psychische en sociale functioneren vindt. Iemands kwaliteit van leven wordt bepaald door verschillende factoren zoals iemands financiële situatie, het gevoel van veiligheid en vrijheid, de kwaliteit van de leefomgeving en van iemands opleiding of gezondheid. Daarnaast kan iemands kwaliteit van leven beïnvloed worden door de cultuur waarin iemand leeft, de religie die iemand aanhangt en zijn of haar verwachtingen, normen en waarden. Het gedeelte van kwaliteit van leven dat bepaald wordt door iemands gezondheid, wordt gezondheidsgerelateerde kwaliteit van leven genoemd. In het Engels wordt gezondheidsgerelateerde kwaliteit van leven "Health-Related Quality of Life" (HRQL) genoemd. Dit proefschrift gaat over de gezondheidsgerelateerde kwaliteit van leven bij patiënten met een voedselallergie.

WAAROM IS HET BELANGRIJK OM KWALITEIT VAN LEVEN TE METEN?

Het is om verschillende redenen belangrijk om de gezondheidsgerelateerde kwaliteit van leven bij patiënten met een voedselallergie te meten. Ten eerste kan het meten van de gezondheidsgerelateerde kwaliteit van leven bij patiënten met een voedselallergie inzicht geven in de verschillende problemen waar patiënten met een voedselallergie mee te maken hebben in het dagelijkse leven. Hierdoor kunnen artsen, diëtisten en verpleegkundigen de patiënten betere adviezen geven voor het omgaan met hun voedselallergie. Ten tweede kunnen kwaliteit van leven metingen gebruikt worden om het effect van interventies te meten vanuit het perspectief van de patiënt. Er kan bijvoorbeeld onderzocht worden wat de invloed is van diagnostische testen op iemands kwaliteit van leven of wat het effect is van nieuwe behandelmethoden op iemands kwaliteit van leven. Uiteindelijk kan dit helpen om de kwaliteit van de diagnostiek of de behandeling te verbeteren en daardoor ook de kwaliteit van leven van de patiënten. Ten derde zijn kwaliteit van leven metingen bij voedselallergie belangrijk, omdat er voor voedselallergie eigenlijk geen objectieve maat bestaat die de voortdurende ernst van voedselallergie weergeeft, zoals bijvoorbeeld de luchtweggevoeligheid bij iemand met astma of de bloedsuikerspiegel bij iemand met suikerziekte. Het is natuurlijk wel mogelijk om de ernst van een allergische reactie weer te geven, maar dan wordt eigenlijk alleen de ernst ten tijde van een allergische reactie gemeten en niet de voortdurende ernst van de voedselallergie. De patiënt heeft namelijk niet alleen last heeft van zijn voedselallergie tijdens een allergische reactie, maar ook in de tussenliggende perioden bijvoorbeeld door de noodzaak om continu alert te zijn op wat hij of zij eet en door de angst voor een ernstige allergische reactie. De voortdurende ernst van voedselallergie (vanuit het perspectief van de patiënt) kan onderzocht worden met kwaliteit van leven metingen.

HOE WORDT KWALITEIT VAN LEVEN GEMETEN?

Gezondheidsgerelateerde kwaliteit van leven kan gemeten worden met vragenlijsten. Er bestaan verschillende typen vragenlijsten: generieke en ziektespecifieke kwaliteit van leven vragenlijsten. Generieke kwaliteit van leven vragenlijsten bevatten vragen over iemands algemene gezondheid, maar geen vragen gericht op één bepaalde ziekte. Deze generieke vragenlijsten zijn bijvoorbeeld heel geschikt om de invloed van verschillende ziekten op gezondheidsgerelateerde kwaliteit van leven met elkaar te vergelijken of om een beeld te krijgen van de gezondheidsgerelateerde kwaliteit van leven van de algemene bevolking. Ziektespecifieke vragenlijsten zijn speciaal ontwikkeld voor één bepaalde ziekte en gaan in op de specifieke problemen van deze ziekte. Deze vragenlijsten zijn daarom juist beter in staat om belangrijke veranderingen in kwaliteit van leven te meten bij patiënten met deze specifieke ziekte. Ziektespecifieke vragenlijsten worden daarom veel gebruikt om inzicht te krijgen in één bepaald ziektebeeld en om het effect van bepaalde behandelingen of diagnostische testen op iemands kwaliteit van leven te onderzoeken. Het hangt dus heel erg af van het doel van het onderzoek welk type vragenlijst het meest geschikt is. Deze vragenlijsten kunnen ingevuld worden door de patiënt zelf. Dit noemt men zelf-rapportages. De vragenlijsten kunnen ook door anderen worden ingevuld (bijvoorbeeld ouders van patiënten met voedselallergie of door medische professionals). In het laatste geval gaat het erom hoe de ander de kwaliteit van leven van de patiënt in schat. Dit noemt men proxy-rapportages. Het behulp van beide rapportages kan men een compleet beeld krijgen van iemands kwaliteit van leven vanuit verschillende perspectieven.

DE VOEDSELALLERGIE EN KWALITEIT VAN LEVEN VRAGENLIJSTEN

Tot voor kort bestonden er nog geen goede ziektespecifieke kwaliteit van leven vragenlijsten voor patiënten met een voedselallergie. Daarom zijn er een aantal jaren geleden, in het kader van een grootschalig Europees onderzoek naar voedselallergie (het EuroPrevall project), drie ziektespecifieke kwaliteit van leven vragenlijsten ontwikkeld in Groningen om kwaliteit van leven te meten bij kinderen (8-12 jaar), tieners (13-17 jaar) en volwassenen (≥18 jaar) met voedselallergie. Iedere leeftijdsgroep heeft een aparte vragenlijst, omdat iedere leeftijdsgroep zijn eigen specifieke problemen kent. De vragenlijsten worden door de patiënt zelf ingevuld (zelf-rapportages). Daarnaast zijn er binnen dit project nog twee ziektespecifieke kwaliteit van leven vragenlijsten ontwikkeld in Ierland en Engeland voor ouders van voedselallergische kinderen (0-12 jaar) en tieners (13-17 jaar). Deze vragenlijsten worden dus door de ouders van de patiënt ingevuld (proxy-rapportages). In het Engels heten deze vijf vragenlijsten the Food Allergy Quality of Life Questionnaires (FAQLQs). De ontwikkeling van de voedselallergie en kwaliteit van leven

vragenlijsten heeft plaatsgevonden met behulp van een speciale methode. De eerste stap van deze methode is het verzamelen van alle mogelijke vragen voor de vragenlijst. Hiervoor werden verschillende bronnen gebruikt zoals patiëntinterviews, literatuurstudies en klinische experts op het gebied van voedselallergie. Vervolgens werden alleen de vragen die het meest belangrijk waren voor patiënten geselecteerd voor de vragenlijsten. Daarna is gekeken of de vragenlijsten valide waren. Onder validiteit wordt verstaan of een vragenlijst meet wat het behoord te meten. Dus meten de vragen dat stukje kwaliteit van leven wat met voedselallergie te maken heeft. Uit al deze onderzoeken is gebleken dat de kwaliteit van leven vragenlijsten voor voedselallergie valide waren, dus dat ze dat meten wat ze behoren te meten. Naast de validiteit van vragenlijsten is het belangrijk dat vragenlijsten betrouwbaar zijn (oftewel reproduceerbaar en consistent) en dat ze in staat zijn om verschillen in kwaliteit van leven te meten over de tijd (responsiviteit). Deze eigenschappen van de voedselallergie en kwaliteit van leven vragenlijsten waren voor de start van dit proefschrift nog niet bekend.

OVERZICHT VAN DIT PROEFSCHRIFT

Dit proefschrift had verschillende doelstellingen. De eerste hoofdstukken (**hoofdstuk 2, 3 en 4**) gaan vooral over de technische eigenschappen van de voedselallergie en kwaliteit van leven vragenlijsten. De laatste hoofdstukken (**hoofdstuk 5, 6 en 7**) gaan meer over de toepassing van de vragenlijsten in de praktijk. Allereerst was het nodig om te onderzoeken of de voedselallergie en kwaliteit van leven vragenlijsten die een paar jaar geleden zijn ontwikkeld betrouwbaar **(hoofdstuk 3),** valide **(hoofdstuk 4 en 7)** en responsief zijn **(hoofdstuk 7)** en dat ze van toegevoegde waarde zijn ten opzicht van de reeds bestaande generieke vragenlijsten **(hoofdstuk 2).** Vervolgens was het nodig om te onderzoeken of de voedselallergie en kwaliteit van leven vragenlijsten die ontwikkeld zijn in Engeland en Ierland ook geschikt zijn voor gebruik in Nederland **(hoofdstuk 5 en 6).** Daarna is onderzocht in hoeverre de meningen van ouders en kinderen (dan wel tieners) wat betreft de kwaliteit van leven van het voedselallergische kind (/tiener) met elkaar overeenkomen en in hoeverre de ouder de kwaliteit van leven van het kind (/tiener) betrouwbaar weer kan geven **(hoofdstuk 5 en 6).** Laatstgenoemde is vooral belangrijk om te weten wanneer het kind (/tiener) zelf niet in staat is om zijn of haar kwaliteit van leven weer te geven, bijvoorbeeld wanneer het kind te jong is of verstandelijk beperkt. In **hoofdstuk 7** wordt beschreven wat de invloed is van de belangrijkste diagnostische test voor voedselallergie (de dubbelblinde placebo-gecontroleerde voedselprovocatie) en de daaropvolgende behandeling op iemands kwaliteit van leven.

SAMENVATTING VAN DE HOOFDSTUKKEN

Hoofdstuk 1 is een algemene introductie op dit proefschrift. Hierin wordt achtergrondinformatie van voedselallergie en kwaliteit van leven weergegeven en hierin worden de doelstellingen van het proefschrift uitgelegd.

Hoofdstuk 2 beschrijft de overeenkomsten en verschillen tussen de generieke en de ziektespecifieke voedselallergie en kwaliteit van leven vragenlijsten. Aan dit onderzoek deden 79 kinderen, 74 tieners en 72 volwassenen mee. Uit het onderzoek bleek dat de ziektespecifieke voedselallergie en kwaliteit van leven vragenlijsten beter geschikt lijken te zijn om verschillen in kwaliteit van leven te meten bij voedselallergische patiënten dan de generieke kwaliteit van leven vragenlijsten. De ziektespecifieke vragenlijsten zijn dus van aanvullende waarde ten opzichte van de generieke vragenlijsten. Ook hebben we onderzocht welke factoren van invloed zijn op kwaliteit van leven bij patiënten met voedselallergie. Hieruit konden we concluderen dat er een sterk verband was tussen de risico-inschatting van een patiënt met betrekking tot de ernst van een allergische reactie en zijn of haar kwaliteit van leven. Dus als een patiënt het risico op een ernstige allergische reactie na een mogelijke inname van het voedingsmiddel heel hoog in schat zal zijn of haar kwaliteit van leven sterk dalen. Deze daling in kwaliteit van leven was dus duidelijk sterker dan wanneer iemand meerdere voedselallergieën heeft of wanneer iemand ergere symptomen heeft tijdens een allergische reactie. Dit bevestigt onze vooronderstellingen dat de subjectieve verwachtingen van patiënten over de mogelijke ernst van een allergische reactie een grotere invloed hebben op iemands kwaliteit van leven dan de meer objectievere maten zoals de ernst van de symptomen tijdens een allergische reactie of het aantal voedselallergieën dat iemand heeft. Dit is belangrijk voor dokters, diëtisten en verpleegkundigen om te weten, omdat zij patiënten eerder neigen te behandelen op basis van de objectieve maten dan op basis van ziektebeleving en kwaliteit van leven.

Hoofdstuk 3 beschrijft de betrouwbaarheid van de voedselallergie en kwaliteit van leven vragenlijsten voor kinderen, tieners en volwassenen. Het is belangrijk om de betrouwbaarheid van een vragenlijst te onderzoeken om te beoordelen of een vragenlijst reproduceerbaar en consistent is. Met andere woorden, wanneer een vragenlijst meerdere malen afgenomen wordt bij dezelfde persoon hoeveel verschil is er dan tussen de ingevulde antwoorden. Voor dit onderzoek hebben ruim 100 patiënten de vragenlijsten twee keer ingevuld met een tussenliggende periode van ongeveer 14 dagen. We konden op deze manier aantonen (met behulp van correlatie coëfficiënten en grafieken) dat de antwoorden die patiënten hebben gegeven op de twee verschillende tijdstippen goed met elkaar overeenkwamen. Dit betekent dat de voedselallergie en kwaliteit van leven vragenlijsten betrouwbaar zijn.

Hoofdstuk 4 is gerelateerd aan de validiteit van de voedselallergie en kwaliteit van leven vragenlijsten en is een vrij technisch hoofdstuk. Met valideren bedoelt men of de voedselallergie en kwaliteit van leven vragenlijsten meten wat ze behoren te meten, namelijk dat stukje kwaliteit van leven dat bepaald wordt door iemands voedselallergie. Normaal gesproken wordt een nieuwe vragenlijst gevalideerd door de nieuwe vragenlijst te vergelijken met een soortgelijke vragenlijst die tot dat moment het best beschikbare instrument is om te meten wat je wilt meten (de gouden standaard). Helaas bestaat er voor kwaliteit van leven vragenlijsten niet een dergelijke gouden standaard. Daarom moest er een nieuw instrument ontwikkeld worden om de voedselallergie en kwaliteit van leven vragenlijsten mee te vergelijken om ze te valideren. Hoofdstuk 4 beschrijft de ontwikkeling en betrouwbaarheid van het instrument dat ontwikkeld is om de voedselallergie en kwaliteit van leven lijsten te valideren, namelijk de Onafhankelijke Maat voor Voedselallergie, oftewel the Food Allergy Independent Measure (FAIM). De FAIM bestaat uit 6 vragen die de risico-inschatting van de patiënt weergeeft wat betreft de ernst van een eventuele toekomstige allergische reactie. De FAIM is dus eigenlijk een vragenlijst die de subjectieve ernst van voedselallergie weergeeft vanuit de beleving van de patiënt. Uit voorgaande onderzoeken is gebleken dat zulke risico-inschattingen en verwachtingen belangrijke voorspellers zijn voor iemands kwaliteit van leven en dus geschikt zijn om kwaliteit van leven vragenlijsten te valideren. Uit de resultaten van hoofdstuk 4 blijkt dat de FAIM een geschikt instrument is om de voedselallergie en kwaliteit van leven vragenlijsten te valideren.

Hoofdstuk 5 beschrijft het verschil in mening tussen ouder en kind wat betreft de impact van voedselallergie op de kwaliteit van leven van het voedselallergische kind (8-12 jaar). Allereerst werd in dit hoofdstuk onderzocht of de Engelse voedselallergie en kwaliteit van leven vragenlijst voor ouders van voedselallergische kinderen (0-12 jaar) geschikt was voor gebruik in Nederland en dat bleek zo te zijn. Vervolgens hebben we de kwaliteit van leven vragenlijsten die door de ouders en hun voedselallergische kind werden ingevuld met elkaar vergeleken. We vonden dat ouders op groepsniveau een betere kwaliteit van leven voor hun kind rapporteerden dan het kind zelf. Deze bevinding suggereert dat de meeste ouders de impact van voedselallergie op hun kind neigen te onderschatten. Tussen voedselallergische tieners en hun ouders **(hoofdstuk 6)** werden ook verschillen in mening gevonden, maar die lagen meer op individueel niveau dan op groepsniveau. Het was bijvoorbeeld zo dat bij het ene ouder-tiener paar de ouder de impact van voedselallergie op de kwaliteit van leven van de tiener als groter in schatte dan de tiener zelf en bij het andere ouder-tiener paar was het juist precies andersom. Op groepsniveau vind je dan geen verschil, omdat deze waarden tegen elkaar uit middelen als je ze bij elkaar optelt. Dus zowel kinderen als tieners verschillen in mening ten opzichte van hun ouders met betrekking tot de impact van voedselallergie op hun kwaliteit van leven, alleen de richting van het verschil (verbetering/verslechtering) in kwaliteit van leven is anders.

Omdat de mening van de ouder over de kwaliteit van leven van hun voedselallergische kind/tiener van invloed is op het besluit van de ouder om wel of niet met hun kind naar een arts te gaan, is het voor medische professionals belangrijk om te realiseren dat ouders de impact van voedselallergie op de kwaliteit van leven van hun kind neigen te onderschatten en dat er tussen ouders en tieners ook wel degelijk verschillen in mening bestaan, maar dan meer op individueel niveau. Om een zo compleet mogelijk beeld te krijgen van de kwaliteit van leven van het kind of de tiener is het dus van belang voor medische professionals om zowel de mening van het kind of de tiener als de mening van de ouder te betrekken bij de medische besluitvoering over de voedselallergische patiënt.

In **hoofdstuk 7** wordt allereerst het onderzoek beschreven dat de longitudinale validiteit en responsiviteit van de voedselallergie en kwaliteit van leven vragenlijsten evalueert. Met responsiviteit wordt bedoeld of de vragenlijsten in staat zijn om verschillen in kwaliteit van leven te meten over de tijd. Met longitudinale validiteit wordt bedoeld of de vragenlijsten valide zijn over de tijd, dus dat ze meten wat ze moeten meten over de tijd, namelijk dat stukje kwaliteit van leven dat bepaald wordt door voedselallergie. Om dit te onderzoeken vulden 235 patiënten de vragenlijsten in 1 maand voor en 6 maanden na een dubbelblinde placebo gecontroleerde voedselprovocatie. Een dergelijke voedselprovocatie is de meest betrouwbare diagnostische test om voedselallergie aan te tonen of uit te sluiten. We hebben voor deze studieopzet gekozen, omdat onze vooronderstelling was dat kwaliteit van leven zou veranderen na het vaststellen of uitsluiten van de diagnose voedselallergie en deze veranderingen in kwaliteit van leven zouden de voedselallergie en kwaliteit van leven vragenlijsten moeten kunnen meten. Uit ons onderzoek bleek dat de vragenlijsten in staat waren om deze verschillen in kwaliteit van leven te meten over de tijd en het bleek ook dat ze valide waren over de tijd. Dit betekent dus dat de voedselallergie en kwaliteit van leven vragenlijsten geschikte instrumenten zijn om kwaliteit van leven bij patiënten met voedselallergie te meten. Omdat er geen andere instrumenten beschikbaar zijn om de voortdurende ernst van voedselallergie te meten, zijn dit belangrijke instrumenten om de impact van bepaalde diagnostische testen en behandelingen op kwaliteit van leven te evalueren. Informatie uit deze studies kan dan gebruikt worden om zulke interventies te verbeteren en daardoor ook de kwaliteit van leven van de patiënt te verbeteren.

Het tweede doel van deze studie was om te onderzoeken wat nou eigenlijk de impact is van een dubbelblinde placebo-gecontroleerde voedselprovocatie op kwaliteit van leven. Uit deze studie bleek dat de kwaliteit van leven van kinderen, tieners en volwassenen met een voedselallergie verbeterde na een negatieve testuitslag van de dubbelblinde voedselprovocatie en de daaropvolgende behandeling (dus na het uitsluiten van de diagnose voedselallergie). Bij kinderen en in mindere mate ook bij volwassenen bleek dat de kwaliteit van leven ook verbeterde na een positieve testuitslag en de daarop volgende behandeling (dus na het aantonen van de diagnose voedselallergie). We denken dat deze verbetering in kwaliteit van leven komt doordat de onzekerheid van

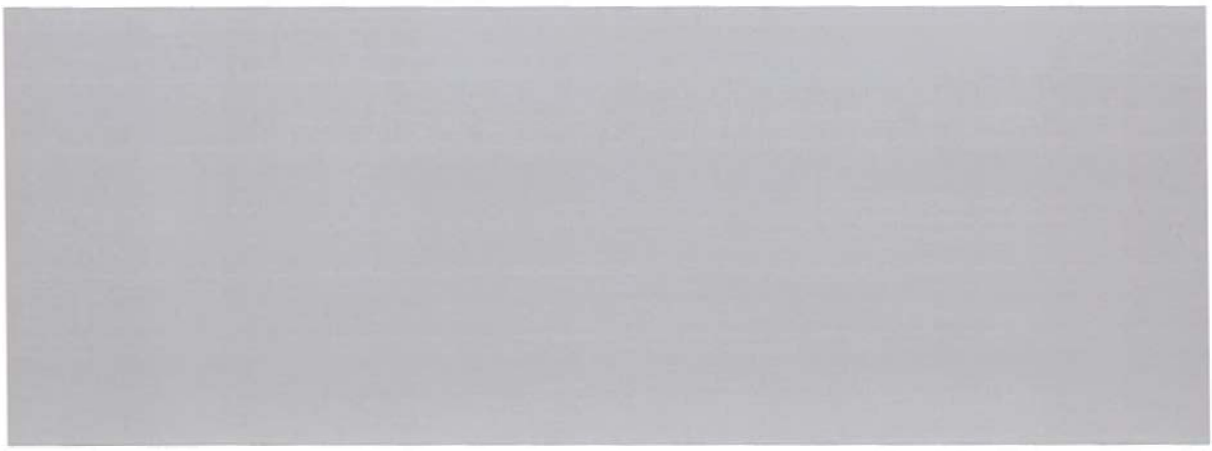
patiënten af neemt en ze beter weten waar ze aan toe zijn. Vervolgens weten ze ook beter welke voedingsmiddelen ze wel en niet moeten vermijden. De grootste verbeteringen in kwaliteit van leven werden gevonden als de diagnose voedselallergie werd uitgesloten. Deze bevindingen bevestigen de grote impact die voedselallergie heeft op het dagelijks leven van patiënten en laten zien welke patiënten baat hebben bij een dubbelblinde placebo gecontroleerde voedselprovocatie.

Het is voor medische professionals ook belangrijk om te weten dat een dubbelblinde placebo-gecontroleerde voedselprovocatie en de daarop volgende behandeling in veel gevallen de kwaliteit van leven van patiënten verbetert, omdat er in het verleden veel discussie geweest is in de literatuur over het tijdrovende proces van deze diagnostische test en de mogelijke lasten van deze test voor de patiënt. Nu gebleken is dat kwaliteit van leven van patiënten juist verbetert na deze diagnostische test, geeft het medische professionals eigenlijk een extra reden om deze diagnostische test juist wel uit te voeren, naast het feit dat deze test de meest betrouwbare test (gouden standaard) is om voedselallergie aan te tonen.

Hoofdstuk 8 geeft een algemene samenvatting en discussie van het hele proefschrift weer.

CONCLUSIE

Dit proefschrift laat zien dat er betrouwbare, valide en responsieve vragenlijsten beschikbaar zijn gekomen om kwaliteit van leven te meten bij kinderen, tieners en volwassenen met een voedselallergie in Nederland. Omdat er geen andere instrumenten beschikbaar zijn om de voortdurende ernst van voedselallergie te meten vanuit het perspectief van de patiënt, zijn dit belangrijke instrumenten om de impact van bepaalde diagnostische testen en behandelingen op kwaliteit van leven te evalueren. Informatie uit deze studies kan dan gebruikt worden om zulke interventies te verbeteren en daardoor ook de kwaliteit van leven van de patiënt te verbeteren. Daarnaast worden deze vragenlijsten momenteel vertaald en gevalideerd in andere landen, zodat kwaliteit van leven bij patiënten met voedselallergie in verschillende culturen met elkaar vergeleken kan worden. Andere belangrijke bevindingen van dit proefschrift zijn dat ouders de impact van voedselallergie op de kwaliteit van leven van hun kinderen (8-12 jaar) neigen te onderschatten en dat ook tieners (13-17 jaar) over dit onderwerp van mening verschillen ten opzicht van hun ouders. Daarnaast werd gevonden dat een dubbelblinde placebo-gecontroleerde voedselprovocatie (de beste test om voedselallergie aan te tonen of uit te sluiten) en de daaropvolgende behandeling de kwaliteit van leven van de meeste patiënten doet verbeteren.



DANKWOORD

"Dokter, wilt u even helpen met de patiënt van kamer 5?", hoorde ik plots een stem achter mij zeggen. Even links achter me kijken en gauw ook even rechts achter me kijken. Nee, daar stond echt niemand anders. Vervolgens met iets luidere stem: "Dokter van der Velde, wilt u nu even helpen met de patiënt van kamer 5?" Langzaam realiseerde ik me dat de verpleegkundige het daadwerkelijk tegen mij had. Ik zei dus wat aarzelend: "Oké, ik kom wel mee…." Dat was in januari 2008. Ben je net goed en wel gewend aan deze nieuwe identiteit van dokter zijn, ben je ineens doctor. Gelukkig scheelt het maar een paar letters. Dat went vast makkelijker….

Alle gekheid op een stokje, "ineens doctor" dat is natuurlijk maar een halve waarheid. Toen het besluit uiteindelijk genomen was om te gaan promoveren, zijn er ontzettend veel mensen bij betrokken geweest om het hele onderzoeksproject tot een succesvol en mooi einde te brengen. Deze mensen kwamen uit verschillende richtingen, zowel deskundigen op het gebied van voedselallergie, als collega's, patiënten, vrienden en familie. Zonder al die mensen was dit proefschrift er nooit gekomen. Daarom ben ik zo blij met dit hoofdstuk uit het proefschrift. Ik maak dus dankbaar gebruik van de gelegenheid om mijn dank uit te brengen.

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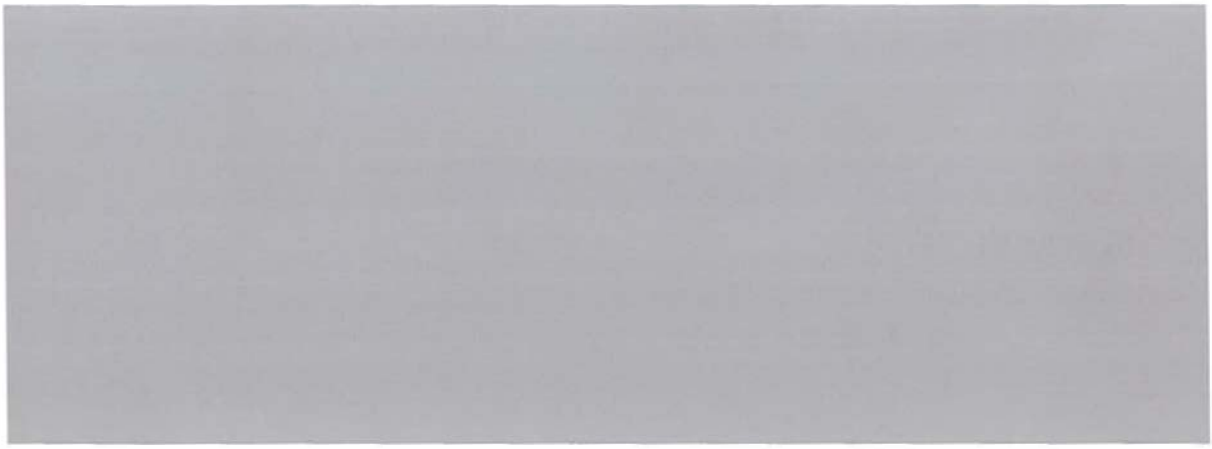
CURRICULUM VITAE

Tina van der Velde werd geboren op 18 augustus 1983 te Hardenberg in Nederland. Zij volgde het lager onderwijs op basisschool de Wiekslag in het Overijsselse Bruchterveld. In 2001 behaalde zij haar Gymnasium diploma aan het Vechtdal College in Hardenberg. Vervolgens ging zij Geneeskunde studeren aan de Rijksuniversiteit van Groningen. In het begin van haar studententijd had zij een bijbaan als assistent-activiteitenbegeleidster bij een sociale werkplaats van een instelling voor mensen met een verstandelijke beperking (de Baalderborg in Hardenberg). Vervolgens had zij een bijbaan als student-assistent bij de PREVEND studie (PREVention of renal ENdstage Diseases). Haar co-schappen volgde zij grotendeels in het Twenteborg Ziekenhuis in Almelo. Zij ging voor een aanvullend co-schap naar het Misikhu Mission Hospital in Kenia en haar keuzeco-schap volgde zij op de spoedeisende hulp in Assen. In 2007 studeerde zij af op "de test-hertest betrouwbaarheid van de voedselallergie en kwaliteit van leven vragenlijsten" en behaalde zij eveneens haar arts-examen. Na haar studie kon zij het onderzoek rond het thema "kwaliteit van leven van patiënten met voedselallergie" als promovenda vervolgen, met dit proefschrift als resultaat. Ook werkte zij daarnaast als basisarts op de spoedeisende hulp in Assen en later als basisarts in een instelling voor mensen met een verstandelijke beperking in Ottersum. Sinds maart 2011 is zij werkzaam als huisarts in opleiding bij de Rijksuniversiteit Groningen.



LIST OF PUBLICATIONS

1. **van der Velde JL**, Flokstra-de Blok BM, Vlieg-Boerstra BJ, et al. Test-retest reliability of the food allergy quality of life questionnaires (FAQLQ) for children, adolescents and adults. Qual Life Res 2009; 18:245-51.
2. **van der Velde JL**, Flokstra-de Blok BM, Vlieg-Boerstra BJ, et al. Development, validity and reliability of the food allergy independent measure (FAIM). Allergy 2010; 65:630-5.
3. Flokstra-de Blok BM, **van der Velde JL**, Vlieg-Boerstra BJ, et al. Health-related quality of life of food allergic patients measured with generic and disease-specific questionnaires. Allergy 2010; 65:1031-8.
4. **van der Velde JL**, Flokstra-de Blok BM, DunnGalvin A, Hourihane JO, Duiverman EJ, Dubois AE. Parents report better food allergy-related quality of life for their food allergic children (8-12 years) than children themselves. Clin Exp Allergy 2011; 41:1431-39.
5. **van der Velde JL**, Flokstra-de Blok BM, Hamp A, Knibb RC, Duiverman EJ, Dubois AE. Adolescent-parent disagreement on health-related quality of life of food-allergic adolescents: Who makes the difference? Allergy 2011; 66:1580-9.
6. **van der Velde JL**, Flokstra-de Blok BM, de Groot H, Oude-Elberink JN, Kerkhof M, Duiverman EJ, Dubois AE. Food allergy-related quality of life after double-blind, placebo-controlled food challenges in adults, adolescents, and children J Allergy Clin Immunol 2012; Jul 24 [Epub ahead of print].
7. Saleh-Langenberg J, Flokstra-de Blok BM, Kemna JC, **van der Velde JL**, Dubois AE. The compliance and burden of treatment with the epinephrine auto-injector in food allergic patients: focus on adolescents. Allergy 2012; Submitted.